Original Article

Crit Care & Shock (2015) 18:97-103

Procalcitonin levels as predictors of neurological outcome in patients with cardiac arrest treated with mild therapeutic hypothermia: a retrospective study

Joseph Varon, Ileana De Anda-Izaguirre, Samantha Fernandez-Hernandez, Alan Padilla Ramos, Cynthia Ocegueda-Pacheco, Santiago M Herrero

Abstract

***Background/objective*: Procalcitonin (PCT) is a biomarker widely used to identify bacterial infections, diagnostic tool for sepsis, monitor response to antibacterial therapy, and to assess general inflammatory response. Our goal was to assess the relationship between PCT levels and neurological outcome in patients who suffered cardiac arrest (CA), and underwent mild therapeutic hypothermia (TH) at 32 °C for a period of 24 hours.**

***Methods*: 55 patients with CA who underwent mild TH were enrolled. Three PCT measurements were obtained (PCT-1 prior to TH, PCT-2 during TH and PCT-3 after TH). Neurological outcome was evaluated with the Cerebral Performance Category (CPC) score. Descriptive statistics and analysis of variance (t-test and ANOVA) were used.**

***Results*: From our cohort, 58.6% had a CPC≥3, 29.3% CPC 1 and 6.9% CPC 2. Mean PCT levels for each group were: PCT CPC 1 2.43 (±3.940 SD), PCT CPC 2 5.49 (±1.516 SD), and PCT CPC≥3 4.077 (±8.805 SD). ANOVA between PCT-1 and CPC scores was F=0.354 (p=0.697), PCT-2 and CPC scores F=0.71 (p=0.501), and PCT-3 and CPC scores F=0.710 (p=0.496).**

***Conclusion*: Our small sample size led to a significant difference of distribution. Further prospective studies with bigger samples are needed in order to obtain better results when assessing the significance of PCT levels as predictors of neurological outcome after CA and TH.**

Key words: Procalcitonin, therapeutic hypothermia, cardiac arrest, neurological outcome.

Introduction

Therapeutic hypothermia (TH) has shown to improve neurological outcome in a variety of settings, such as traumatic brain injury, neonatal encephalopathy and drowning events, but mainly in patients who suffer cardiac arrest (CA) with return of spontaneous circulation (ROSC). (1,2) However, an ideal predictor to anticipate a good neurological outcome is not yet well established. (1) The search for the "holy grail" of serum biomarkers to predict the neurological outcome after CA has been intensified over the past 10 years, and a number of studies have been conducted focusing on finding a useful predictor. The main biomarkers currently under study are: S-100β, neuron-specific enolase (NSE), glial fibrillary acid protein (GFAP), C-reactive protein (CRP), and procalcitonin (PCT). (1-4)

PCT, the pro-hormone of calcitonin, is normally produced in the parafollicular C-cells of the thyroid gland and neuroendocrine cells of the lung and intestine. Normal values in humans are <0.1 ng/mL and they increase within 2 to 4 hours in severe forms of systemic inflammation and bacterial infections. (5) PCT levels remain considerably elevated until recovery, and therefore, can be used as an accessible and cost-effective diagnostic tool. Currently accepted uses for PCT include: stratification of bacterial sepsis, distinction of bacterial vs. viral infections (i.e., meningitis and community acquired pneumonia) and antibiotic response moni-

From University General Hospital, The University of Texas Health Science Center at Houston, The University of Texas Medical Branch at Galveston, Dorrington Medical Associates, PA, Houston, Texas, USA (Joseph Varon), Dorrington Medical Associates, Universidad Autónoma de Baja California, Campus Tijuana, School of Medicine, Houston, Texas, USA (Ileana De Anda-Izaguirre, Alan Padilla Ramos), Dorrington Medical Associates, Universidad Popular Autónoma del Estado de Puebla, Campus Puebla, School of Medicine, Houston, Texas, USA (Samantha Fernandez-Hernandez), Dorrington Medical Associates, Hospital Angeles Valle Oriente, Monterrey, Mexico (Cynthia Ocegueda-Pacheco), and The Jilin Heart Hospital, Changchun City, China (Santiago M Herrero).

Address for correspondence:
Joseph Varon, MD, FACP, FCCP, FCCM, FRSM
2219 Dorrington Street
Houston, Texas, 77030, USA
Tel: +1-713-669-1670
Fax: +1-713-669-1671
Email: joseph.varon@uth.tmc.edu

toring. (5-8)
Recently PCT has been thought to be a biomarker to predict neurological outcome after CA. (4) This concept was first proposed by Fries and associates in 2003, when analyzing PCT and S-100β serum levels in 23 successfully resuscitated patients after out-of-hospital cardiac arrest (OHCA) the following 3 days after hospitalization. (4) PCT levels were significantly higher at days 1-3 in patients with a bad neurological outcome, and the authors concluded that this biomarker's elevation was independent from sepsis or severe forms of infection in the setting of CA. (4) In 2006, Adib-Conquy and collaborators compared PCT and soluble triggering receptor expressed on myeloid cells 1 (sTREM-1) levels in patients with sepsis that had undergone cardiac surgery and had suffered OHCA. (9) Two relevant findings were reported in this study: 1) Peak PCT plasma levels in patients who died after CA and in those with severe sepsis were markedly similar, and 2) PCT wasn't increased in CA survivors but was significantly elevated in the group of patients who died after CA (p=0.003 in the group that died from neurological failure and p=0.0003 in the group that died from shock). (9) The authors concluded that PCT wasn't specific for sepsis, and more than likely elevated as a response to acute systemic inflammation. (9)
Hayashida and coworkers years later demonstrated PCT's superiority compared to glial fibrillary acidic protein (GFAP) in this field, but it wasn't until 2011 that Stammet and collaborators stated that "PCT might be an ancillary marker for outcome prediction after CA treated with induced hypothermia". In this study, no patient regained consciousness when a PCT level was >16 ng/ml. (10-11)
Our study aimed to asses PCT as a prognosticator for neurological outcome in post CA patients who underwent mild TH.

Methods

This multicentric, retrospective, observational study was performed using data obtained from two different Academical Medical Centers: University General Hospital in Houston, Texas, USA and Hospital de Cabueñes in Gijón, Asturias, Spain. An Institutional Reviewer Board granted permission to conduct this study.
We included medical records from patients who suffered in and OHCA with ROSC and were treated with mild TH, hospitalized in these facilities between 2013 and 2014. Our inclusion criteria were: a) ≥18-year-old, b) absence of pulse and cardiopulmonary resuscitation (CPR) given, c) ROSC, d) treatment with mild TH (32-33 °C) using Thermogard XP® ZOLL, e) recorded PCT levels obtained upon arrival, before TH and after 24 hrs of TH and f) recorded Cerebral Performance Category (CPC) score. Medical records that reported a known source of infection or sepsis were automatically excluded. A final cohort of 55 medical records was analyzed.

Outcome measurements and treatments related

To assess our primary hypothesis, we used PCT levels and CPC scores as the dependent and independent variables. Mild TH was the primary treatment directly affecting our variables that did not require to be statistically assessed.

CPC score

The CPC score was calculated based on previously published data. (12) For analytic purposes, we divided the CPC scores into groups: good, mild and poor neurological outcome. In the CPC 1 group (good neurological outcome) we included patients with CPC 1, in the CPC 2 group those with CPC 2, and in the CPC≥3 group (poor neurological outcome), those with CPC 3-5. CPC score was measured within 2 weeks after TH was completed.

Procalcitonin

Three different PCT measurements were recorded in each of the patients: 1) Prior to treatment with mild TH (PCT-1), 2) During mild TH (PCT-2) and 3) 24 hours after mild TH (PCT-3). PCT levels were measured using the Thermo Scientific™ B·R·A·H·M·S PCT™ (Waltham, Massachusetts, USA) and LUMItest®-PC.

Therapeutic hypothermia

TH was done in compliance with the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care in each patient after ROSC. (13) Mild TH was performed at a goal temperature of 32 °C, achieved with intravascular cooling device Thermogard XP® ZOLL. (14) The duration of TH was 24 hours, and re-warming was achieved at a rate of 0.1 °C/hr.

Data analysis

Our main goal was to describe the correlation between PCT levels and neurological outcome in post CA patients. In order to assess this linear correlation we divided our cohort into 3 different groups: CPC 1, CPC 2 and CPC 3. Descriptive statistics was used among the groups, describing continuous data, frequencies, mean values and standard deviations.

Despite the non-parametric distribution of our data, we used linear correlation statistics, One-way ANOVA to compare variances between PCT levels and CPC scores and t-test to compare variances between PCT levels and age, as well as time of ROSC.

Results

From the 55 patients enrolled, 78.2% (n=43) were male, 21.8% (n=12) were female, with a mean age of 63.11 (±14.58 SD) (**Table 1**). The mean time of ROSC was 21.42 min (±10.78 SD), from which 63.6% was <25 min and 36.4% >25 min. The cardiac rhythms presented were: 25 (45.5%) ventricular fibrillation, 19 (34.5%) asystole, and 11 (20%) other rhythms. Twenty nine point three percents of the patients had a good neurological outcome (CPC 1), 6.9% had mild neurological outcome (CPC 2) and 58.6% had a poor neurological outcome (CPC≥3) (**Table 1**).

Mean PCT-1 was 2.66 ng/mL (±8.585 SD), mean PCT-2 4.098 ng/mL (±7.67 SD) and mean PCT-3 3.026 ng/mL (±5.045 SD). The mean PCT level for each CPC group was also obtained; patients with good neurological outcome PCT CPC 1 had a mean PCT of 2.43 ng/mL (±3.940 SD), the ones with mild neurological outcome PCT CPC 2 had a mean PCT of 5.49 ng/mL (±1.516 SD) and those with poor neurological outcome PCT CPC≥3 4.077 ng/mL (±8.805 SD) (**Table 2**). We observed higher levels of PCT in patients with mild and poor neurological outcome, as compared to the group who had a good neurological outcome.

For PCT-1 a variance between groups of 27.47 with a higher variance within groups of 75.49 led to a ratio (F) of 0.364 (p=0.697). For PCT-2 the variance between groups was 41.78, lower than a variance within groups of 59.579 with an F 0.701 (p=0.501). Lastly, for PCT-3 the variance between groups was 18.271, lower than the variance within groups of 25.736 with an F 0.710 (p=0.496) (**Table 3**).

Secondary analyses were performed using t-test so that age and ROSC were assessed. Patients with an age >65 were not correlated with elevated PCT levels in each PCT group (PCT-1 p=0.416, PCT-2 p=0.200 and PCT-3 p=0.148), whereas ROSC >25 min was correlated with a higher PCT mean (PCT-1 p=0.042, PCT-2 p=0.063 and PCT-3 p=0.098) (**Table 4**).

Discussion

Several studies have already established the ability of PCT to diagnose the presence of inflammation and infection, mainly in critically ill patients. (15,16) However, its use as a predictor of neurological outcome has only recently been studied. It is well known that after ROSC a second process of injury occurs, the so-called post-cardiac arrest syndrome (PCAS) or post-resuscitation syndrome. It is the combination of 3 main processes: post-CA brain injury, post-CA myocardial dysfunction and post-CA reperfusion injury, leading to a sepsis/systemic inflammatory response syndrome (SIRS)-like syndrome, that in the end it will give rise to PCT. (17,18) Previous studies have shown an increase in serum levels of PCT, particularly during the first 48 hours after an ischemic insult, in those patients who have suffered CA with worse neurological outcome and higher mortality rate. (19) Even though our PCT was not measured after 48 hours exactly, the time elapsed since the ischemic insult and the initiation of TH was prolonged enough for elevation of PCT to start. This explains our results and the difference of levels between each PCT group, as seen on **Table 2**.

Despite our higher PCT levels being seen on PCT during TH, the PCAS could explain this elevation, since the exact time elapsed after the CA and initiation of TH was not recorded on patients' medical records.

Our results showed an F-ratio of 0.364 (p=0.697) for PCT-1, F 0.701 (p=0.501) for PCT-2 and F 0.710 (p=0.496) for PCT-3, meaning that there was no statistical significance, explained by our insufficient sample size (**Table 3**).

To reinforce our hypothesis, we performed secondary analyses to address the relationship between the age and PCT levels as well as ROSC and PCT levels. We hypothesized that the higher the age and the more prolonged the ROSC, the higher the PCT levels would be. Age did not correlate with PCT levels, unlike ROSC, as seen on **Table 4**. Previous studies have not shown a correlation between age and PCT levels either. (20)

On the other hand, t-test showed that ROSC >25 min was directly correlated with higher PCT levels, proving that the longer the ischemic insult, the more severe the PCAS would be. In addition, our study showed that PCT-1, PCT-2 and PCT-3 means were significantly higher in patients with CPC 3, less elevated in those with CPC 1, and even less elevated in those with CPC 2.

The ischemic insult was prolonged and extensive enough to highly elevate PCT levels during the first measurement in all CPC score groups, but this stopped in the CPC 1 group once TH was started. In a comprehensive review published by Polderman, it was stated that the effects of TH on the mitigation of destructive processes caused by PCAS

are divided into early and late mechanisms, therefore, a drop in a biomarker for inflammation would be expected, such as PCT, once TH is implemented and the early effects of TH start taking place. (18) Some of the most important effects of this therapy, such as decrease in production of free radicals, decreased neuroexcitotoxicity, as well as decrease in cerebral metabolism (6-10% by every 1 °C drop) and mitochondria dysfunction, are presumed to be early mechanisms, which would explain the drop in PCT levels in the CPC 1 group. (21)

Study limitations

Some limitations were found in this study. The small sample size we had, with a cohort of 55 patients, led to several issues. When the means of each PCT were obtained, they seemed as if they were, in fact, correlated with the neurological outcome, however, when the results were statistically analyzed, there was no significance due to the marked variance seen. Similar studies have been done with bigger sample sizes and positive significant results. (11) Another bias appeared since this was a retrospective study, the veracity of the data could not be trust completely, (i.e. knowing if the physicians treating these patients followed a standardized post-resuscitation algorithm or if changes were made at any point, exact times at which PCT levels were measured before, during and after TH).

Conclusion

We concluded that the fact there is not a statistical significance between mean PCT levels does not completely reject our hypothesis that PCT levels are correlated with neurological outcome. Our small sample size led to a significant difference of distribution between each CPC score group and in the end it gave us a ratio <1 with ANOVA test. Further prospective studies and multicenter trials, with more significant samples, are advised to be done in order to obtain more reliable and significant results when assessing the correlation between PCT levels and neurological outcome after suffering CA and being treated with TH. These trials, along with previously published data and the data presented in this study, will aid in finding a more conclusive result for this subject.

Table 1. Descriptive statistics and means

	N	Mean/%	SD
Gender			
• Female	12	21.8%	-
• Male	43	78.2%	-
Age	55	63.1	±14.581
ROSC	55	21.4	±10.789
• >25 min	20	36.4%	-
• <25 min	35	63.6%	-
Rhythm			
• As	19	34.5%	-
• VF	25	45.5%	-
• Other	11	20.0%	-
CPC score			
• CPC 1	17	29.3%	-
• CPC 2	4	6.9%	-
• CPC 3	34	58.6%	-

Table 2. Mean PCT levels

	Mean (SD)
PCT-1	2.66±8.585
PCT-2	4.098±7.675
PCT-3	3.026±5.045
PCT-CPC 1	2.430±3.940
PCT-CPC 2	0.792±1.516
PCT-CPC≥3	4.077±8.805

Table 3. One way Anova testing

		Mean (SD) 95% CI	M2 between	M2 within	F	p (<0.08)
PCT-1	CPC 1	1.64±2.534	27.471	75.492	0.364	0.697
	CPC 2	0.59±0.475				
	CPC 3	3.43±10.762				
PCT-2	CPC 1	3.55±5.399	41.785	59.579	0.701	0.501
	CPC 2	0.21±0.205				
	CPC 3	4.83±8.930				
PCT-3	CPC 1	2.10±3.290	18.271	25.736	0.710	0.496
	CPC 2	1.58±2.614				
	CPC 3	3.66±5.889				

Table 4. Secondary analysis t-test

PCT level variances among age	Above 65	Below 65	t-test
PCT-1	3.65 (±11.976)	1.71 (±2.716)	p=0.416
PCT-2	5.48 (±9.982)	2.76 (±4.255)	p=0.200
PCT-3	4.053 (±6.578)	2.03 (±2.677)	p=0.148
PCT level variances among ROSC	>25 min	<25 min	t-test
PCT-1	5.76 (±13.764)	0.896 (±1.527)	p=0.042
PCT-2	6.64 (±10.424)	2.64 (±5.184)	p=0.063
PCT-3	4.51 (±6.583)	2.17 (±3.763)	p=0.098

References

1. Pfeifer R, Franz M, Figulla HR. Hypothermia after cardiac arrest does not affect serum levels of neuron-specific enolase and protein S-100b. Acta Anaesthesiol Scand. 2014;58:1093-100.
2. Larsson IM, Wallin E, Kristofferzon ML, Niessner M, Zetterberg H, Rubertsson S. Post-cardiac arrest serum levels of glial fibrillary acidic protein for predicting neurological outcome. Resuscitation 2014;85:1654-61.
3. Dell'anna AM, Bini Vinotti J, Beumier M, Orbegozo-Cortes D, Donadello K, Scolletta S, et al. C-reactive protein levels after cardiac arrest in patients treated with therapeutic hypothermia. Resuscitation 2014;85:932-8.
4. Fries M, Kunz D, Gressner AM, Rossaint R, Kuhlen R. Procalcitonin serum levels after out-of-hospital cardiac arrest. Resuscitation 2003; 59:105-9.
5. Dandona P, Nix D, Wilson MF, Aljada A, Love J, Assicot M, et al. Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab 1994;79:1605-8.
6. Jekarl DW, Kim JY, Lee S, Kim M, Kim Y, Han K, et al. Diagnosis and evaluation of severity of sepsis via the use of biomarkers and profiles of 13 cytokines: a multiplex analysis. Clin Chem Lab Med 2015;53:575-81.
7. Johansson N, Kalin M, Backman-Johansson C, Larsson A, Nilsson K, Hedlund J. Procalcitonin levels in community-acquired pneumonia - correlation with aetiology and severity. Scand J Infect Dis 2014;46:787-91.
8. Oliveira CF, Botoni FA, Oliveira CR, Silva CB, Pereira HA, Serufo JC, et al. Procalcitonin versus C-reactive protein for guiding antibiotic therapy in sepsis: a randomized trial. Crit Care Med 2013;41:2336-43.
9. Adib-Conquy M, Monchi M, Goulenok C, Laurent I, Thuong M, Cavaillon JM, et al. Increased plasma levels of soluble triggering receptor expressed on myeloid cells and procalcitonin after cardiac surgery and cardiac arrest without infection. Shock 2007;28:406-10.
10. Hayashida H, Kaneko T, Kasaoka S, Oshima C, Miyauchi T, Fujita M, et al. Comparison of the Predictability of Neurological Outcome by Serum Procalcitonin and Glial Fibrillary Acidic Protein in Postcardiac-Arrest Patients. Neurocrit Care 2010;12:252-7.
11. Stammet P, Devaux Y, Azuaje F, Werer C, Lorang C, Gilson G, et al. Assessment of Procalcitonin to Predict Outcome in Hypothermia-Treated Patients after Cardiac Arrest. Crit Care Res Pract 2011;2011:631062.
12. Jennett B, Bond M. Assessment of outcome after severe brain damage. The Lancet 1975;1: 480-4.
13. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, et al. Part 9: Post-Cardiac Arrest Care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122: S768-86.
14. Kory P, Fukunaga M, Mathew JP, Singh B, Szainwald L, Mosak J, et al. Outcomes of Mild Therapeutic Hypothermia After In-Hospital Cardiac Arrest. Neurocrit Care 2012;16:406-12.
15. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993;341:515-8.
16. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: A systematic review and meta-analysis: Crit Care Med 2006;34:1996-2003.
17. Nolan JP, Morley PT, Hoek TLV, Hickey RW. Therapeutic hypothermia after cardiac arrest. An advisory statement by the Advancement Life support Task Force of the International Liaison committee on Resuscitation. Resuscitation 2003;57:231-5.
18. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med 2009;37:S186-202.
19. Polderman KH, Varon J. Cool hemodynamics - The intricate interplay between therapeutic hypothermia and the post-cardiac arrest syndrome. Resuscitation 2014;85:975-6.
20. Stein M, Schachter-Davidov A, Babai I, Tasher D, Somekh E. The Accuracy of C-Reactive Protein, Procalcitonin, and s-TREM-1 in the Prediction of Serious Bacterial Infection in Neonates. Clin Pediatr (Phila) 2015;54: 439-44.
21. Annborn M, Dankiewicz J, Erlinge D, Hertel S, Rundgren M, Smith JG, et al. Procalcitonin after cardiac arrest - An indicator of severity of illness, ischemia-reperfusion injury and outcome. Resuscitation 2013;84:782-7.