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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Emergency Medicine / Acil Tıp

The Relationship Between Serum Levels of Procalcitonin, Lactate, HgA1c and Functional Outcome in Acute Ischemic Stroke Patients

Zuhal Kalyon Karaman[1], Çiğdem Özpolat[2], Özge Ecmel Onur[2], Haldun Akoğlu[2], Arzu Denizbaşı[2]

[1]Şanlıurfa Mehmet Akif İnan Eğitim ve Araştırma Hastanesi, Acil Tıp, Şanlıurfa, Türkiye

[2]Marmara Üniversitesi, Acil Tıp, İstanbul, Türkiye

Zuhal KALYON KARAMAN, MD
Çiğdem ÖZPOLAT, Asst. Prof.
Özge ECMEL ONUR, Prof. Dr.
Haldun AKOĞLU, Prof. Dr.
Arzu DENİZBAŞI, Prof. Dr.

Correspondence: Özge Onur
Marmara Üniversitesi, Acil Tıp, İstanbul, Türkiye
Phone: -
E-mail: ozberkozge@gmail.com

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ABSTRACT

Objectives: Prognostic parameters in stroke management are important for emergency department physicians to reduce mortality and morbidity. No parameters could be determined for prognosis in acute stroke. In this study, we aimed to determine whether serum procalcitonin (PCT), lactate and HgA1c levels at admission and changes of PCT and lactate levels in 2 hours were associated with short-term functional outcome (3rd day) after acute ischemic stroke.

Materials and Methods: This was a prospective observational prognostic test study. All consecutive patients admitted to the emergency department and diagnosed as the first episode of acute ischemic stroke were included in the study. On admission and 2nd hour, PCT and lactate levels and admission HgA1c levels were collected from all subjects. Our primary aim was to correlate these values with the Modified Rankin Scale (mRS) which shows the functional outcome. Our secondary aim was determining correlation with mortality on the 3rd day and to determine their predictive value.

Results: There was no statistically significant difference between the favorable (mRS <2) and non-favorable groups in terms of PCT and lactate values and PCT and lactate clearances. There was a statistically significant difference between the two groups in terms of HgA1c value. When the threshold value analysis was performed to determine the non-favorable outcome, the threshold value was determined as 5.7.

Conclusion: Our results demonstrate that ischemic stroke patients with higher levels of HgA1c at the time of initial presentation have an increased risk for poor functional neurological outcome (high mRS) on the 3rd day. We couldn't analyze mortality due to the low patient number.

Keywords: procalcitonin, lactate, HgA1c, stroke

İskemik Serebrovasküler Olay Geçirmiş Hastalarda Hemoglobin A1c, Laktat, Prokalsitonin Seviyelerinin Fonksiyonel Sonuç ile İlişkisi

ÖZET

Amaç: İnme yönetiminde prognostik parametrelerin ortaya konması, acil servis hekimleri için mortalite ve morbiditeyi azaltmada önemlidir. Akut inmede prognoz için belirlenebilmiş herhangi bir parametre bulunamamıştır. Bu çalışmada, serum prokalsitonin(PCT), laktat ve HgA1c düzeylerinin başvuru sırasındaki ve PCT ve laktat düzeylerinin 2 saat içindeki değişikliklerinin akut iskemik inmeden sonra kısa dönem fonksiyonel sonuçla (3. gün) ilişkili olup olmadığını belirlemeyi amaçladık.

Hastalar ve Yöntem: Bu prospektif gözlemsel prognostik test çalışmasıydı. Ardışık tüm hastalar çalışmaya dahil edildi. Giriş ve 2. saatte tüm deneklerden PCT ve laktat seviyeleri ve giriş HgA1c düzeyleri toplandı. Bu değerleri 3. günde Modifiye Rankin Skalası (mRs) ve mortalite ile ilişkilendirmeyi ve prediktif değerlerini belirlemeyi amaçladık.

Bulgular: İyi (mRS <2) ve kötü sonlanımlı gruplar arasında PCT ve laktat değerlerinin kendileri ile PCT ve laktat değer değişimleri açısından istatistiksel olarak anlamlı bir fark bulunamadı. İki grup arasında geliş HgA1c değeri açısından istatistiksel olarak anlamlı bir fark vardı. Olumsuz sonucu belirlemek için eşik değer analizi yapıldığında, eşik değer 5.7 olarak belirlendi.

Sonuç: Çalışma sonuçları, ilk başvuru sırasında daha yüksek HgA1c düzeyi olan iskemik inme hastalarının 3. günde kötü fonksiyonel nörolojik sonuç risk artışı olduğunu göstermiştir.

Anahtar Kelimeler: Prokalsitonin, Laktat, HgA1c, inme

Ischemic stroke is the third leading cause of mortality and morbidity in most countries in the world[1]. An assessment of early risk with an estimation of the severity and prognosis is necessary for ideal care and effective use of health care sources to improve outcomes (2).

Inflammatory processes have the main roles in stroke in both the etiology and the pathophysiology of cerebral ischemia (3). Procalcitonin (PCT) is known as a useful marker to discriminate infection from inflammation and has recently become popular as an early marker for sepsis. Recent research have targeted the relationship between serum levels of PCT and atherosclerotic diseases (3,4).

Lactate is traditionally seen as a marker of ischemia and a waste product of anaerobic glycolysis. In acute stroke, accumulation of lactate in ischemic regions of the brain has been documented, both in animal models and patients (5,6).

Hyperglycemia or diabetes mellitus is a known risk factor for stroke and pre-ischemic hyperglycemia and was found to aggravate the post-ischemic outcome. Most clinical studies have concluded that hyperglycemia predicts increased stroke mortality independently of age, stroke type, and severity (7,8).

In this study, we aimed to determine whether serum PCT, lactate and HgA1c levels at admission were associated with short-term functional outcome (3rd day) after acute ischemic stroke (AIS). Up to date, none of the current studies searched for this acute period. The secondary aim was to investigate the changes of PCT and lactate levels in the emergency department period (2 hours) and to evaluate the relationship between these changes and the short-term functional outcome.

Material and Method

This was a single-center, prospective observational study performed in the emergency department (ED) of a training and research hospital between June 2016 – October 2017. The study has been approved by the university ethics committee.

Patients were eligible for inclusion if they were admitted to the ED with the onset of symptoms within 24 h and diagnosed and treated as AIS defined according to the American Heart Association (AHA) (9).

Patients were excluded if they were aged < 18, pregnant, had cerebrovascular disease (CVD) history, arrested?! (had a cardiac arrest) in the ED, intracranial hemorrhage on cranial CT, systemic infections or malignancy. They were also excluded if they had thrombolysis or thrombectomy treatment. Written informed consent was obtained from the patients or their next of kin.

Patients were initially evaluated by the ED physician and then the neurology attending physician. AIS was confirmed by neurologic examination, and cranial imaging showed ischemic lesions compatible with the clinical findings.

Patient forms were recorded including their demographic information, physical examination findings and medical histories. On admission, routine blood samples including PCT, lactate and HgA1c were collected from all subjects. Blood samples were re-collected 2 hours later to check the changes of lactate and PCT levels.

In our study, the Bio-Rad kit was used as the HgA1c kit. The procalcitonin kit is the Roche brand Elecsys Brahms. Radiometer ABL 735 Blood Gas Analyzer was used for lactate levels.

Functional outcome was obtained on the 3rd day after admission according to the modified Rankin Scale (mRS). Outcome assessment was performed by using medical records or by telephone interviews on the 3rd day of admission. Functional outcome was defined as favorable if the mRS score was 0 to 2 and non-favorable if higher than 2.

The study cohort was prospectively followed up for mortality. On the 3rd day of admission, patients were checked for mortality using medical records or telephone interviews.

Statistical Analysis

Continuous variables were reported with means and standard deviations (95% confidence intervals (CI)) or medians and interquartile ranges (IQR) according to their distribution patterns. Mann–Whitney U and student t-test were used to compare independent groups. Categorical variables were reported with frequencies and percentages. Categorical variables were compared with the chi-squared test. Index test Hgb A1c levels were analyzed by a receiver operating characteristic curve (ROC) to assess their prognostic utility in estimating short-term mortality. The area under the curve (AUC, accuracy), sensitivity,

specificity, and likelihood ratios were reported with their 95% CIs. MedCalc Statistical Software version 18 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org) was used for all analyses.

STARD 2015 guidelines for reporting of diagnostic accuracy studies were used as a reference while preparing for this report (10).

Results

During the study period, 258 patients with AIS were screened. A total of 90 patients enrolled in the study (Figure 1). The median age was 72 (62-79) years. The male ratio was slightly higher (%55.6), vital signs and comorbid diseases are as seen in Table 1.

Of the patients included in the study, 18 (20%) had an mRS score of 0-2 (as a favorable outcome group) (Table 2).

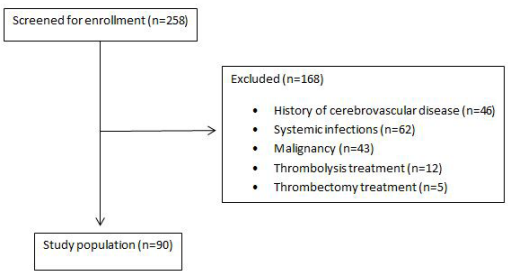

Figure 1. Study Flowchart

The median lactate level of the 90 patients included in the study was found to be 1.9 mmol / L (IQR: 1.6-2.4). The median lactate value of 18 patients in the favorable outcome group was 2.0 mmol / L, while the median lactate value of 72 patients in the non-favorable outcome group was determined as 1.9 mmol / L. There was no statistically significant difference between these groups (p: 0.8955). Median lactate level was found to be 1.76 (IQR: 1.4 / 2.4) at the second hour of the same patients. The lactate clearance of these patients was calculated as -0.2 (IQR: -0.4 / 0.2). The median lactate clearance of the patients in the group with a favorable outcome was calculated as -0.30 mmol / L. The median lactate clearance value was calculated as -0.20 in the non-favorable outcome group. There was no statistically significant difference between the two groups in terms of lactate clearance (p: 0.2221) (Table 1, Table 3).

Table 1. Demographics, vital parameters on admission, lab parameters and medical history of patients

Demographics	Total
Age (years), median (IQR)	72 (62 - 79)
Male, n (%)	50 (55.6)
Vital Signs, median (IQR)	
SBP (mmHg)	152 (130 - 175)
DBP (mmHg)	89.5 (80.0, 99.0)
HR (bpm)	88 (76 – 101)
Temperature (C)	36.5 (36.1 - 36.6)
RR (/min)	16 (14 - 18)
SaO2 (%) Oxygen saturation	96.5 (96.0 – 97.0)
Medical history, n (%)	
DM	36 (40)
HT	56 (62.2)
CAD	19 (21.1)
Lab	
Lactate admission (mmol/L), median(IQR)	1.90 (1.60- 2.40)
Lactate 2nd hour (mmol/L), median(IQR)	1.75 (1.40- 2.40)
Lactate clearance(mmol/L), median(IQR)	-0.20 (-0.40-0.20)
PCT admission (ng/ml), median(IQR)	0.05 (0.03- 0.08)
PCT 2nd hour(ng/ml), median(IQR)	0.05 (0.03-0.08)
PCT clearance(ng/ml), median(IQR)	0.00 (-0.01-0.01)
HgA1c (n:77), median(IQR)	5.80 (5.30-6.73)

IQR: interquartile range, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, RR: respiratory rate, SaO2: Oxygen saturation, DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, PCT: Procalcitonin

Table 2. mRS of groups

mRS	n (%)		n (%)
0	2 (2.2)	favorable	18 (20)
1	5 (5.6)		
2	11 (12.2)		
3	23 (25.6)	non-favorable	72 (80)
4	20 (22.2)		
5	28 (31.1)		
6	1 (1.1)		

mRS: Modified Rankin Scale

In our study, the median value of PCT was 0.05 ng / mL (IQR: 0.03 / 0.08). The median PCT value of 18 patients in the favorable outcome group was 0.04, while the median PCT value of 72 patients in the non-favorable outcome group was 0.055. There was no statistically significant difference in PCT values between the two groups (p: 0.2905). The median value of procalcitonin was found to be 0.05 ng / mL (IQR: 0.03 / 0.08) at the 2nd hour of the same patients.

The PCT clearance of these patients was 0.00 (IQR: -0.01 / 0.01). The median PCT clearance was calculated as 0.00 in patients with favorable or non-favorable outcome groups. There was no statistically significant difference between the two groups in terms of PCT clearance (p: 0.6002) (Table 1, Table 3).

Table 3. Median lactate, PCT and HgA1c values of groups

Laboratory Values	Favorable			Non-Favorable			
	n	median	Average Rank	n	median	Average Rank	P*
Lactate (mmol/L)	18	2.0	44.78	72	1.9	45.68	0.8955
PCT	18	0.04	39.72	72	0.055	46.94	0.2905
Δ Lactate (mmol/L)	18	-0.30	38.78	72	-0.20	47.18	0.2221
Δ PCT	18	0.00	42.64	72	0.00	46.22	0.6002
HgA1c (n:77)	15	5.40	27.97	62	5.90	41.67	0.0332

PCT: Procalcitonin

In our study, the HgA1c values of 77 patients were reached. The HgA1c median value of 77 patients was determined to be 5.8 (IQR: 5.3-6.7). The HgA1c value of 3 patients in the favorable outcome group could not be reached, and the median HgA1c value of 15 patients was found to be 5.4. The median HgA1c value of 62 patients in the non-favorable outcome group was determined as 5.9 and the HgA1c value of 13 patients could not be reached. There was a statistically significant difference between the two groups in terms of HgA1c value (p: 0.033) (Table 1, Table 3). Of the diabetic patients, 30 patients had HgA1c values. Four of the patients were in the non-favorable group (mean HgbA1c was 6.20) and 26 were in the favorable group (mean HgbA1c was 7.25). There was no difference in HgA1c between the groups of diabetic patients. Of the non-diabetic patients, 47 had HgbA1c values.

Eleven of them were in the non-favorable group, and the mean HgbA1c levels were 5.30; 36 were in the favorable group and the HgbA1c levels were 5.65. There was a significant difference between the groups (0.046).

The discriminative values of HgA1c levels for the prediction of non-favorable outcome were investigated with the use of ROC curve analysis. Serum HbA1c levels significantly discriminate non-favorable outcome with an AUC of 0.678 (p: 0.0206) (Figure 2).

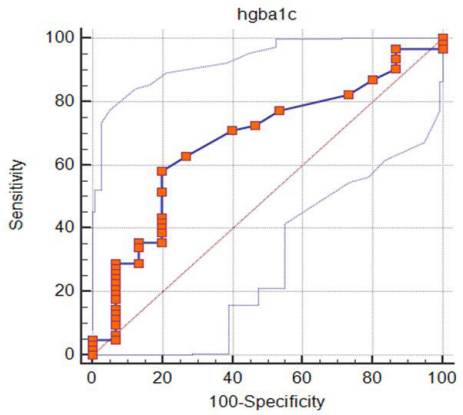

Figure 2. ROC curve of neurological outcome according to HgA1c values and mRS score

Then, when the threshold value analysis was performed to determine the non-favorable outcome, the threshold value was determined as 5.7 according to the Youden index. The sensitivity was 58.065% (44.847% -70.485%) and the specificity was 80.000% (51,911% -95.699%). The area under the threshold is 0.690 (0.575 - 0.791). The prevalence of the disease was 80.519% (69.913% - 88.667%). The positive predictive value was 92.308% (81.014% - 97.122%) and negative predictive value was 31.579% (23.862% - 40.465%) (Figure 3).

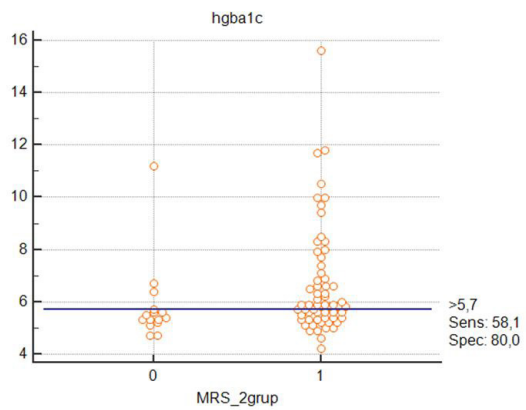

Figure 3. Threshold analysis of HgA1c level in poor outcome

Only one of our patients died in a 3 day follow-up period.

Discussion

Our results demonstrate that ischemic stroke patients with higher levels of HgA1c at the time of initial presentation to the ED have an increased risk for poor functional neurological outcome on the 3rd day. Whereas initial

serum PCT and lactate levels and also changes in the acute period do not predict short term functional outcome in patients with acute stroke.

Some studies found that PCT levels were associated with the presence and functional outcome of atherosclerotic disease (1,4). Tian et al showed that serum PCT levels were significantly elevated in case of acute ischemic stroke as compared with control cases (11). They concluded that elevated levels of PCT could be considered as a diagnostic marker for ischemic stroke. Also in 2015, a study reported that the PCT level of AIS patients at admission was an independent predictor of long-term (1 year) mortality (12). In our study, serum PCT levels at admission did not correlate with short-term neurologic outcomes. But probably 3rd day functional score was too early for consideration for PCT. Miyakis et al studied PCT and searched the prognostic value of PCT. They found that serial PCT levels did not correlate with stroke mortality or neurologic outcome at discharge (13). They found the highest median PCT level was recorded on days 2 and 3. No statistically significant differences were observed for the comparison of PCT values between individual days. Serial serum PCT levels did not correlate with stroke mortality or neurologic outcome at discharge in their study, too. A statistically significant association was observed between cases exhibiting peak PCT levels on day 7 and the presence of fever. In our study, we excluded patients who had a systemic infection. Maybe this was the reason that we could not found any correlation for serum PCT levels at admission or acute term PCT change, with short-term neurologic outcome in this study.

In hypoperfusion states, lactate may be produced and efflux by anaerobic glycolysis in affected neuronal cells (14,15). But the blood-brain barrier permeability of lactate is low and blood and CSF lactate balance slowly with the aid of monocarboxylate transporters (16). Brouns et al showed that lactate levels in CSF—but not in the blood—can be used as a reliable marker for the metabolic crisis in acute ischemic stroke and correlate with poor outcome (17). Whereas Jo et al found that initial hyperlactatemia represents an independent risk factor for the poor outcome at 3months (6). In this study, serum lactate levels at admission did not correlate with short-term neurologic outcomes. In the acute period, CSF lactate may be a better indicator of local metabolism than blood lactate.

HgA1c is an indicator of chronically elevated blood glucose levels associated with DM or insulin resistance. Sunaga et al showed that the relationship of the risk of stroke, especially ischemic stroke, to HbA1c in the general population appears to be graded without any apparent threshold (7). They concluded that the ischemic stroke risk would increase from a relatively mild HbA 1c level of ≥ 6.0%. Cloonan et al stated that this plasma metabolite marks the state of endothelial dysfunction and predicts the severity of white matter hyperintensity in patients with ischemic stroke (8). In another study, it was shown that increased HgA1c increased poor outcome and mortality in ischemic stroke (18). Mansur et al showed that hyperglycemia, acute or chronic, was associated with increased mortality and worse clinical outcomes in AIS patients treated with tPA (19). The relationship was found nonlinear, with a plateau observed at glucose levels above 200 mg/dL and HbA1C levels above 8.0% in their study. Kocaman et al showed that an HgbA1C level above 6% is correlated with recurrent ischemic stroke, too (20). Our study also indicates a relationship between HbA1c level and short-term outcome (3 rd day) in ischemic stroke patients and a level above 5.7% was found to be a risk factor for poor outcome. These findings provide evidence that chronic hyperglycemia may influence the prognosis of acute ischemic stroke patients.

There are some limitations in this study. We studied only the baseline 0 and 2nd hour measurement for PCT and lactate levels and therefore cannot clarify the variability of the PCT levels during all courses of ischemic stroke. We have a small sample size in one centre. Therefore, our results might not be generalizable.

Conclusion

Short term (3rd day) outcome is poorer in ischemic stroke patients with higher HbA1c levels on admission. We couldn't find such an association with admission and 2 nd hour PCT and lactate levels.

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