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Rapid Report

Mortality prediction of ischemic stroke patients without thrombectomy by blood total antioxidant capacity

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It has been previously established that total antioxidant capacity concentrations of blood on the first day of ischemic stroke could predict mortality. Therefore, our study objective was to determine whether total antioxidant capacity concentrations in the blood during the first week of a cerebral infarction could help predict mortality. We included severe and malignant middle cerebral artery infarction patients (affecting 50% or more of the territory in computed tomography and a score of nine or fewer points in the Glasgow Coma Scale). Serum total antioxidant capacity concentrations were determined on days first, fourth, and eighth of the diagnosis of a malignant middle cerebral artery infarction. Higher serum total antioxidant capacity concentrations at first ($P < 0.001$), fourth ($P < 0.001$), and eighth ($P = 0.003$) day were found in non-surviving patients than in surviving ones. Serum total antioxidant capacity concentrations on first, fourth and eighth day of malignant middle cerebral artery infarction had an area under curve (95% Confidence Intervals) for 30-day mortality prediction of 0.86 (0.75-0.93; $P < 0.001$), 0.87 (0.74-0.95; $P < 0.001$) and 0.79 (0.64-0.90; $P = 0.004$)), respectively. Thus, the potential use of serum total antioxidant capacity concentrations at any time during the first 7 days of a severe malignant middle cerebral artery infarction without thrombectomy to predict mortality was the main novel finding of our study.

Keywords

Total antioxidant capacity; prognosis; ischemic stroke; blood-brain barrier

1. Introduction

A high number of disabilities, resource consumption, and deaths result from ischemic stroke (Powers et al., 2018). Oxidative stress can produce secondary brain injury in ischemic stroke, and antioxidants are generated to avoid cell damage due to reactive oxygen species (Manzanero et al., 2013; Olmez and Ozyurt, 2012; Pradeep et al., 2012; Radak et al., 2014; Rodrigo et al., 2013; Warner, 2004). The different antioxidant molecules act synergistically, and determining total antioxidant capacity (TAC) could provide better information on antioxidant status than the determination of each antioxidant compound separately (Ghiselli et al., 2000).

There is scarce data on blood TAC concentrations and prognosis of patients with ischemic stroke (Fernández-Gajardo et al., 2019; Ghonimi et al., 2019; Guldiken et al., 2009; Lorente et al., 2016; Lorenzano et al., 2018, 2019). One study found lower blood TAC concentration measured on the first day of ischemic stroke in patients with poor functional prognosis (Ghonimi et al., 2019). In contrast, higher blood TAC concentrations have been found on the first day of ischemic stroke patients than in healthy subjects (Guldiken et al., 2009), and in non-surviving patients than in surviving ones (Lorente et al., 2016). Another study found no association between blood TAC concentrations during the first week of ischemic stroke and the infarct volume (Fernández-Gajardo et al., 2019). On the other hand, no significant differences were found in plasma TAC concentrations within 9 hours of stroke onset between patients with infarct growth and those without (Lorenzano et al., 2018), while statistically significant differences were observed in plasma TAC concentrations within 9 hours of stroke onset between patients with ischemic penumbra (perfusion-weighted/diffusion-weighted mismatch $>$ 20%) and those without (Lorenzano et al., 2019). Therefore, our study aims to determine whether blood TAC levels during the first seven days of a cerebral infarction can help in mortality prediction.

2. Methods

2.1 Design and subjects

Our perspective and observational study was developed in the Intensive Care Unit of six Spanish hospitals after the approval of the Institutional Ethical Board of all hospitals and with the written informed consent of a family member of each patient.

We included severe and malignant middle cerebral artery infarction (MMCAI) patients, which affected 50% or more of the territory in computed tomography and had ≤ 9 points in Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974). Exclusion criteria were sepsis, autoimmune disease, malignant disease, pregnancy, brain hemorrhage, or under 18 years of age. The patients were recruited between 2009-2012 by the intensivist physician in charge of the patient when the patient met the criteria for recruitment.

Previously, we had determined serum concentrations of TAC on the first day of severe MMCAI in 58 patients (Lorente et al., 2016). We then determined serum malondialdehyde concentrations on days one, four, and eight of a severe MMCAI in 68 patients (Lorente et al., 2019). For this research, we determined serum TAC concentrations on days one, four, and eight in those 68 severe MMCAI patients to determine its potential capability for mortality prediction and its potential association with lipid peroxidation, assessed by blood malondialdehyde concentrations (Dalle-Donne et al., 2006; Draper and Hadley, 1990).

2.2 Clinical and demographic variables on day 1

Age, sex, body temperature, diabetes mellitus, sodium, arterial hypertension, fraction inspired of oxygen ($FI0_2$), pressure arterial of oxygen (PaO_2), platelets, hemoglobin, fibrinogen, international normalized ratio (INR), leukocytes, activated partial thromboplastin time (aPTT), bilirubin, creatinine, glycemia, lactic acid, GCS, Acute Physiology and Chronic Health Evaluation II (APACHE II) score (Knaus et al., 1985) were recorded. Decompressive craniectomy, thrombolysis, midline shift, volume infarction, hemorrhagic transformation, and 30-day mortality (as an end-point study) was also recorded.

2.3 Measurement of serum TAC on days first, fourth and eighth of severe MMCAI

We obtained serum blood samples on days one, four, and eight of severe MMCAI diagnosis and froze them at -80 °C until blood determinations. Total antioxidant capacity was assessed using kits from Cayman Chemical Corporation (Ann Arbor, USA), which has a detection limit of 0.04 mmol/L, intra-assay coefficient of variations of 3.4% and inter-assay coefficient of variations of 3.0%. The determinations were carried out in the Laboratory Department of the Canary University Hospital (Tenerife, Spain), and laboratory personnel was blinded to patient demographics and clinical characteristics.

2.4 Statistical methods

We used frequencies (percentages) and medians (interquartile ranges) to describe categorical and continuous variables. We compared continuous and categorical variables between surviving patients and non-surviving ones by Wilcoxon-Mann-Whitney and chi-square tests.

We carried out receiver operating characteristic analyses to test the capacity to predict mortality of serum TAC concentrations on days one, four, and eight of MMCAI, and the area under the curve from serum TAC concentrations was reported each day. The optimal cut-off values for each day were selected based on the Youden J index. As deceased patients were 34, we performed two regression model analyses with 4 variables in each model to test the association between serum TAC levels and 30-day mortality controlling for different variables, in the first model controlling for variables that had significant univariate associations with 30-day mortality (platelet count, GCS, and lactic acid) and in the second model controlling for known risk factors of death after stroke (age, sex, baseline blood glycemia). We have not included APACHE-II due to its inclusion of GCS and age. Friedman test was used to test differences in serum TAC concentrations at days one, four, and eight within the groups of surviving and non-surviving patients. $P < 0.05$ values were considered as significant.

3. Results

We analyzed 34 non-surviving and 34 surviving patients. We found higher GCS and platelets in surviving patients than in the non-survivors (Table 1). We found no statistically significant differences in 30-day survival rate in patients without decompressive craniectomy (48%, 25 of 52 patients) or with it (56%, 9 of 16 patients) (P = 0.78), nor in patients without intravenous thrombolysis (50%, 23 of 47 patients) or with it (52%, 11 of 21 patients) (P = 0.99). No patients underwent endovascular thrombectomy. A total of 14 patients died after cardiac arrest, 2 after nosocomial pneumonia, and 18 patients to brain death.

Higher serum TAC concentrations on days one ($P < 0.001$), four ($P < 0.001$), and eight (P = 0.003) were found in non-surviving patients in comparison to surviving ones (Fig. 1). No significant differences were found in serum TAC concentrations at days one, four, and eight within the groups of surviving (P = 0.37) and non-surviving (P = 0.26) patients.

To predict the mortality at 30 days serum TAC concentrations on days one, four and eight of the MMCAI had an area under the

Table 1. Biochemical and clinical characteristics of survivor and non-survivor patients. Variables are expressed as number (percentage) or median (percentile 25-75).

	Survivors (n = 34)	Non-survivors (n = 34)	*P*-value
Gender female	14 (41.2)	13 (38.2)	0.99
Arterial hypertension	19 (55.9)	16 (47.1)	0.63
Diabetes mellitus	4 (11.8)	9 (26.5)	0.22
Age (years)	59 (47-68)	63 (53-70)	0.36
Temperature (°C)	36.4 (36.0-37.0)	36.9 (36.0-37.3)	0.15
GCS score	7 (6-8)	6 (3-7)	0.01
Sodium (mEq/L)	139 (136-145)	140 (139-145)	0.38
Bilirubin (mg/dl)	0.60 (0.40-0.83)	0.60 (0.33-1.10)	0.95
Lactic acid (mmol/L)	1.20 (0.90-1.70)	1.55 (1.00-2.70)	0.05
Creatinine (mg/dl)	0.80 (0.60-1.13)	1.00 (0.70-1.25)	0.19
Glycemia (g/dL)	127 (100-170)	136 (118-162)	0.40
PaO2 (mmHg)	156 (105-293)	115 (94-267)	0.26
PaO2/FI0_2 ratio	300 (198-369)	254 (192-325)	0.24
Platelets x10^3/mm^3	202 (171-265)	175 (136-216)	0.02
Hemoglobin (g/dL)	12.1 (11.4-14.0)	12.5 (11.0-14.8)	0.81
Leukocytes x 10^3/mm^3	12.4 (9.6-16.9)	13.9 (9.7-20.1)	0.32
INR	1.06 (1.00-1.20)	1.20 (1.01-1.31)	0.07
Fibrinogen (mg/dl)	443 (416-489)	419 (337-631)	0.90
aPTT (seconds)	28 (25-30)	27 (26-32)	0.91
APACHE-II score	20 (16-25)	22 (19-27)	0.06
Thrombolysis	11 (32.4)	10 (29.4)	0.99
Decompressive craniectomy	9 (26.5)	7 (20.6)	0.78
Haemorrhagic transformation	7 (20.6)	6 (17.6)	0.99
Volume infarction (ml)	173 (100-231)	180 (60-277)	0.64
Midline shift (mm)	6.0 (2.5-11.5)	9.0 (3.5-15.0)	0.43
TAC (mmol/mL)	2.30 (1.89-3.29)	6.10 (3.56-12.08))	< 0.001

GCS = Glasgow Coma Scale; PaO_2= pressure arterial of oxygen; FIO_2= fraction inspired of oxygen; APACHE II = Acute Physiology and Chronic Health Evaluation; INR = international normalized ratio; aPTT = activated partial thromboplastin time; TAC = total antioxidant capacity.

curve (95% CI = confidence intervals) of 0.86 (0.75-0.93; $P < 0.001$), 0.87 (0.74-0.95; $P < 0.001$) and 0.79 (0.64-0.90; $P = 0.004$)), respectively. Table 2 showed positive and negative likelihood ratios, sensitivity, specificity, positive, and negative predicted values of serum TAC concentrations cut-offs on days one, four, and eight of MMCAI for predicting mortality.

Regression analyses showed an association of serum TAC levels with 30-day mortality controlling for platelet count, GCS and lactic acid (Odds ratio = 2.672; 95% CI = 1.489-4.796; $P = 0.001$), and also controlling for sex, glycemia and age (Odds ratio = 1.969; 95% CI = 1.288-3.011; $P = 0.002$) (Table 3).

We found an association between serum concentrations of TAC and malondialdehyde at days one ($\rho = 0.46$; $P \leq 0.001$), four ($\rho = 0.49$; $P \leq 0.001$), and eight ($\rho = 0.65$; $P \leq 0.001$) of a severe MMCAI.

4. Discussion

The potential use of serum concentrations of TAC during the first week of severe MMCAI for predicting mortality was the main novel result in our study. On the one hand, no association was found between infarct growth and plasma TAC concentrations within 9 hours of stroke onset (Lorenzano et al., 2018), and between infarct size and blood TAC concentrations during the first week of ischemic stroke (Fernández-Gajardo et al., 2019); however, the association between blood TAC concentrations and mortality was not studied. Also, another study found lower blood TAC concentration on day 1 of ischemic stroke in patients with poor functional prognostic (Ghonimi et al., 2019). On the other hand, an association between high plasma TAC concentrations within 9 hours of stroke onset and brain ischemic penumbra has been found (Lorenzano et al., 2019). Previously, we had determined blood TAC concentration on the first day of an MMCAI, and we found higher concentrations in 30-day non-surviving patients (Lorente et al., 2016). Therefore, the determination of serum TAC concentrations at fourth and eighth day of MMCAI is a new aspect in our study.

Furthermore, higher serum TAC concentrations also at days four and eight of severe MMCAI in non-surviving patients were novel findings in our study. Another interesting and new finding in our study for clinicians was that serum TAC concentrations in the first week of severe MMCAI could be used to predict mortality. These novel findings from our study may be due to our inclusion of patients only with an acute infarction $\geq 50\%$ in the middle territory and with GCS ≤ 9.

Another interesting and new finding in our study was the correlation between lipid peroxidation (estimated by serum concen-

Table 2. Receiver operation characteristic analyses for prediction of mortality at 30 days by serum total antioxidant capacity (TAC) levels at days 1^{st}, 4^{th} and 8^{th} in survivor and non-survivor patients.

	2 Day 1^{st}	**3 Day 4^{th}**	**4 Day 8^{th}**
Cut-off of TAC (mmol/mL)	> 3.31	> 2.81	> 3.13
Sensitivity (95% CI)	79 (62-91)	89 (65-98)	75 (43-95)
Specificity (95% CI)	79 (62-91)	82 (66-93)	91 (76-98)
Negative likelihood ratio (95% CI)	0.3 (0.1-0.5)	0.2 (0.1-0.5)	0.3 (0.1-0.7)
Negative predicted value (95% CI)	79 (66-84)	93 (79-98)	91 (79-97)
Positive likelihood ratio (95% CI)	3.9 (2.0-7.6)	5.0 (2.4-10.6)	8.5 (2.7-26.3)
Positive predicted value (95% CI)	79 (66-84)	73 (56-85)	75 (49-90)

CI: confidence intervals

Table 3. Multiple logistic regression analysis for mortality prediction.

Variable	**Odds Ratio**	**95% Confidence Interval**	*P*
First model			
TAC (mmol/mL)	2.672	1.489-4.796	0.001
Platelet count (each 1,000/mm^3)	0.986	0.974-0.998	0.03
Glasgow Coma Scale (points)	0.721	0.487-1.066	0.10
Lactic acid (mmol/L)	1.205	0.628-2.312	0.57
Second model			
TAC (mmol/mL)	1.969	1.288-3.011	0.002
Sex (male vs. female)	1.533	0.386-6.088	0.54
Age (years)	1.017	0.967-1.070	0.51
Glycemia (g/dL)	1.004	0.994-1.014	0.42

TAC: total antioxidant capacity

trations of malondialdehyde) and serum TAC concentrations during the first week of severe MMCAI. A study has found higher plasma TAC concentrations and higher oxidative stress, assessed by plasma concentrations of nitric oxide metabolite levels (nitrite and nitrate), in diabetic acute stroke patients than in healthy control subjects (Guldiken et al., 2009). We propose like Guldiken et al. (2009) that the high serum TAC concentrations in ischemic stroke patients and non-surviving patients and its correlation with lipid peroxidation may be due to high reactive oxygen species production, and an attempt to avoid those harmful effects.

The blood-brain barrier (BBB) is a selective semipermeable border that separates peripheral blood and neural brain tissue in the central nervous system. The BBB restricts the passage of pathogens and large or hydrophilic molecules and the impermeability of the BBB has hampered the use of antioxidants agents for neuroprotection (Rashid et al., 2014). However, some murine model studies have shown that after the oral administration of tea, different substances of tea are brain permeable and have neuroprotective effects (by increasing antioxidant capacity in brain samples) (Pervin et al., 2019; Rashid et al., 2014). Oxidative stress and antioxidant capacity in brain samples have been reduced in cerebral ischemia animal models with melatonin administration (Blanco et al., 2017; Kryl'skii et al., 2019). Also, oxidative stress measured in plasma has been reduced by different antioxidant vitamins administered orally in patients with acute ischemic stroke (E, C, B2, B6, B12) (Ullegaddi et al., 2004, 2005, 2006). It is possible that the BBB damage that occurs in cerebral ischemia (and that could contribute to hemorrhagic transformation) (Li et al., 2019) could favor the passage of those substances through BBB and reduce oxidative stress in cerebral ischemia. We found high serum concentrations of TAC and malondialdehyde concentrations in non-survivor patients; however, we have not assessed antioxidant capacity and oxidative stress in brain samples in our study.

The 2007 American guidelines on ischaemic strokes (Adams et al., 2007) suggested the use of intravenous thrombolysis therapy in patients without multilobar infarction in CT (hypodensity in a third of cerebral hemisphere). The improved outcome with thrombectomy is unclear, and in severely affected patients due to malignant edema, decompressive surgery is recommended. The American guidelines of 2018 (Powers et al., 2018) suggested the use of intravenous thrombolysis therapy in patients with an ischemic injury involving less than one-third of the middle cerebral artery territory; the use of thrombectomy in patients with occlusion of the internal carotid artery or middle cerebral artery infarction segment 1, pre-stroke modified Rankin scale $\leq$ 1, age $\geq$ 18 years, Alberta Stroke Program Early Computed Tomography Score $\geq$ 6, National Institutes of Health Stroke Scale $\geq$ 6, and treatment initiated within 6 hours of symptom onset; and the use of decompressive craniectomy in patients with $\leq$ 60 years of age, unilateral middle cerebral artery infarction and neurological impairment within 48 hours despite medical therapy. In our series (anterior to the new recommendations of the 2018 American Guidelines) only MMCAI patients without thrombectomy treatment had no significant differences in the survival rate and this was found between patients with or without intravenous thrombolysis, and with or without decompressive craniectomy.

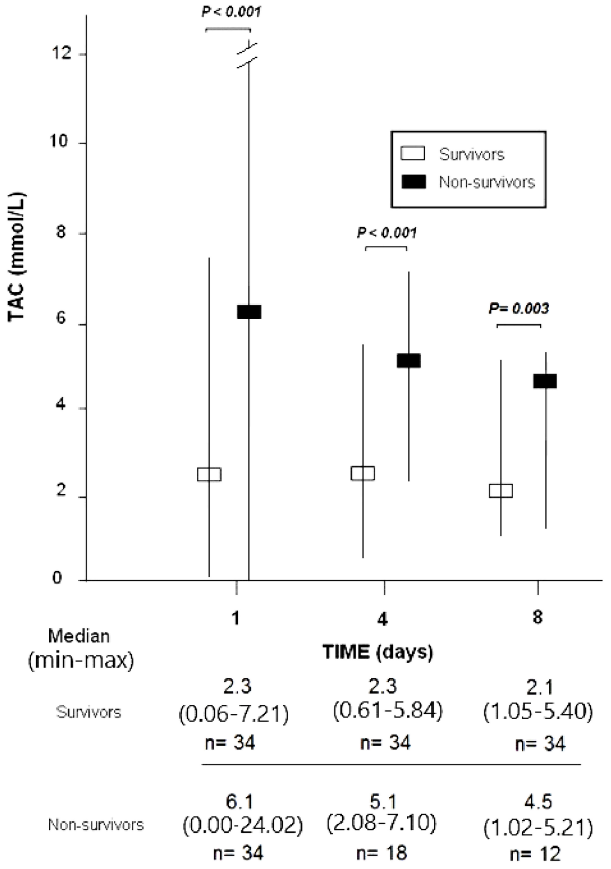

Fig. 1. Serum total antioxidant capacity (TAC) at days 1^{st}, 4^{th} and 8^{th} in survivor and non-survivor patients.

There are some limitations in our study. We have not recorded the time interval from the onset of stroke to blood draws for the TAC measurement, to surgical intervention, and to hemorrhagic transformation to evaluate whether those factors could modify serum TAC levels. We have not registered the number and causes of exclusion and the percentage of severe MMCAI about the total ischemic stroke patients. Patients with autoimmune diseases or sepsis were excluded from the study, and we did not find differences in renal or hepatic functions at inclusion between surviving and non-surviving patients; however, data on atrial fibrillation, coronary artery disease, smoking and dyslipidemia which could influence serum TAC levels were not provided.

We chose to include only patients with severe MMCAI because of the higher mortality in that group of patients (50% in our series). Serum TAC levels could have potential predictive capabilities within the population under study; however, the results of this study are not generalizable to all strokes due to exclusion criteria. Also, the results of this study need to be replicated by another team before using them in the prediction of mortality due to the scarce and contradictory data on blood TAC concentrations and prognosis of patients suffering from ischemic stroke. We think that the interest of this study is not only that serum TAC concentrations could potentially predict mortality, but also to explore the effect of new modalities of treatment in this subgroup of patients at high risk of mortatility.

5. Conclusions

The potential use of serum TAC concentrations at any time during the first 7 days of a severe MMCAI infarction without thrombectomy to predict mortality was the main novel finding of our study.

Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation; aPTT: activated partial thromboplastin time; FIO_2: fraction inspired of oxygen; GCS: Glasgow Coma Scale; ICU: Intensive Care Unit; INR: International normalized ratio; PaO_2: pressure arterial of oxygen; TAC: total antioxidant capacity.

Author contributions

LL coordinated and designed the project, and drafted the article. JJC, JSV, MA, MMM, LRG, VGM, and RS participated in data recollection. PAG, APC, and AFGR performed blood determinations. AJ participated in data interpretation. Finally, the manuscript was critically revised and approved by all authors.

Ethics approval and consent to participate

Our perspective and observational study were developed in the Intensive Care Unit of six Spanish hospitals after the approval of the Institutional Ethical Board of all hospitals and with the written informed consent of a family member of each patient.

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Conflict of Interest

The authors have not competing interests.

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