Selected biomarkers of oxidative stress in ischemic stroke

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According to WHO, stroke is a clinical syndrome characterized by a sudden onset of focal symptoms or generalized brain dysfunction that persist - if not fatal beforehand - longer than 24 hours and have no other cause than a vascular one. It is one of the most common causes of death after cancer and myocardial infarction, and the leading cause of disability in the world. Oxidative stress and the inflammatory response are believed to play a critical role in the pathogenesis of acute ischemic stroke. Reactive oxygen species (ROS) produced during the ischemia and reperfusion phases of acute ischemic stroke (AIS) can damage the brain by attacking the cerebral vessels, damage macromolecules in cellular components such as cellular proteins, membrane lipids and nucleic acids. Brain tissue is particularly sensitive to ROS due to the low level of endogenous antioxidant enzymes. One of the important non-enzymatic antioxidants is melatonin, the pineal gland hormone which, in addition to modulating the circadian rhythm, also has anti-inflammatory properties.

The aim of our study was to evaluate the temporal profile of the melatonin metabolite 6-hydroxymelatonin sulphate (6-SM) in the urine and carbonyl groups in the serum of patients with acute ischemic stroke treated with intravenous thrombolysis.
The study included 123 patients aged 57 to 81 years with acute ischemic stroke who were admitted to the Department of Neurology of the University Hospital in Bydgoszcz with indications for thrombolytic treatment. Urine melatonin levels and serum protein carbonyl concentration were measured by ELISA using a commercial Immuno Biological Laboratories kit.

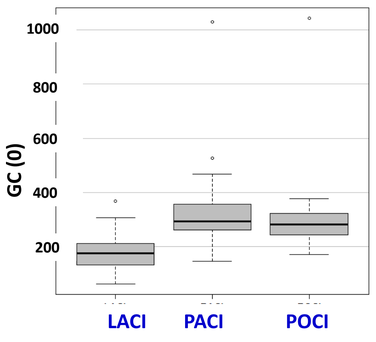
There were also statistically significant differences between the values of melatonin and carbonyl groups compared to the control group. Melatonin concentration measured < 4.5 h on the 1st and 7th day after stroke was statistically lower and the concentration of carbonyl groups was higher than in the group of healthy people were observed.

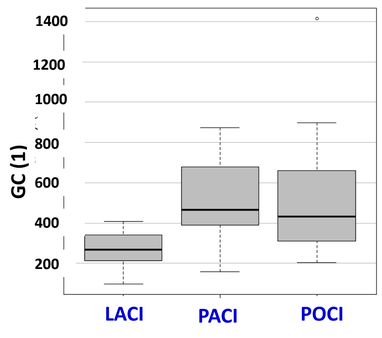
Biomarker	Patients group	Control group (n = 22)	P-value
CG (0) [Q1, Q3] [U/mL]	222.02[171.09, 283.47] (n = 81)	144.18[93.49, 191.69]	< 0.001
CG (1) [Q1, Q3] [U/mL]	355.56[224.98, 437.38] (n = 37)	144.18[93.49, 191.69]	< 0.001
CG (2) [Q1, Q3] [U/mL]	195.08[124.21, 242.01] (n = 34)	144.18[93.49, 191.69]	0.032

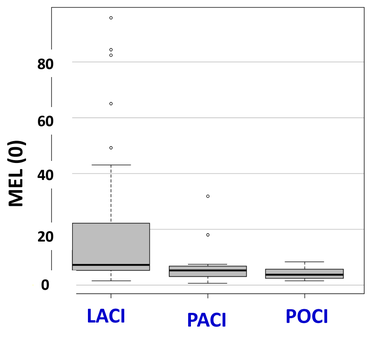
Biomarker	Patients group	Control group (n = 23)	P-value
MEL (0) [Q1, Q3] [pg/mL]	6.41[4.26, 8.64] (n = 77)	37.85[21.46, 103.82]	< 0.001
MEL (1) [Q1, Q3] [pg/mL]	9.34[5.49, 25.42] (n = 44)	37.85[21.46, 103.82]	< 0.001
MEL (2) [Q1, Q3] [pg/mL]	9.61[6.04, 15.53] (n = 31)	37.85[21.46, 103.82	< 0.001

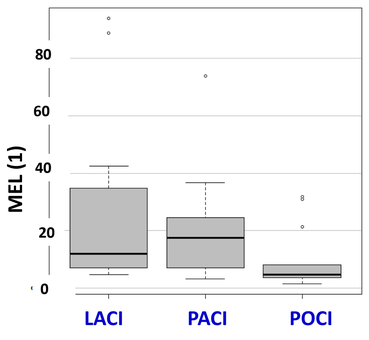
CG (0) – concentration of carbonyl groups determined within 4.5 hours; CG (1) – concentration of carbonyl groups determined within 24 hours; CG (2) – concentration of carbonyl groups determined within 7 days.
MEL (0) – concentration of melatonin determined within 4.5 hours; MEL (1) – concentration of melatonin determined within 24 hours; MEL (2) – concentration of melatonin determined within 7 days.

The significant statistical correlation between melatonin concentration and carbonyl groups in patients with AIS were detected. The significant statistical connection between MEL measured in < 4.5 hours and on the first day after the stroke and the concentration of carbonyl groups determined after one week (R = 0.42, R = 48) were detected. There was also a weak negative correlation between the levels of melatonin and carbonyl groups during < 4.5 hours from the stroke (R = - 0.26).
MEL assessed in time < 4.5 h were statistically higher in patients suffering from the LACI (lacunar cerebral infarct) ischemic stroke in comparison to the patients with POCI (posterior circulation infarction) and PACI (partial anterior circulation infarct) strokes (7.27 vs 5.32 pg/mL, $p = 0.008$; 7.27 vs 3.73 pg/mL, $p < 0.001$, respectively). Additionally, statistical differences were found for LACI and PACI concerning MEL determined on day 1 (11.84 vs 4.72, $p = 0.02$) . The concentration of carbonyl groups during < 4.5 h and on the first day after stroke showed statistically significant differences between the values of this biomarker in patients with LACI stroke and patients with POCI and PACI strokes (176.89 vs 292.84, $p < 0.001$; 176.89 vs 282.67, $p < 0.001$; 268.42 vs 464.87, $p = 0.006$; 268.42 vs 432.49 U/mL, $p = 0.013$, respectively).

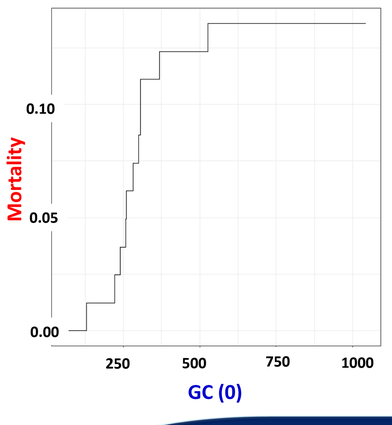


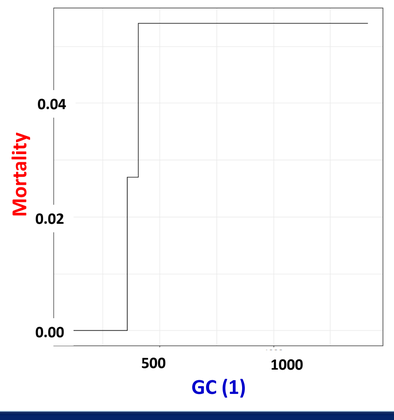


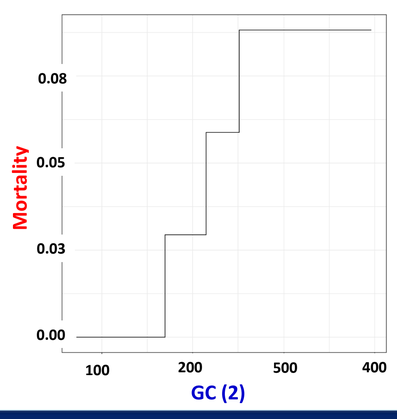


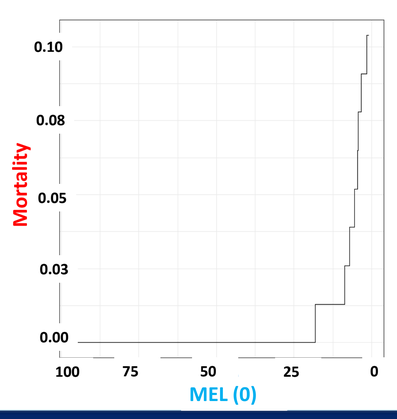


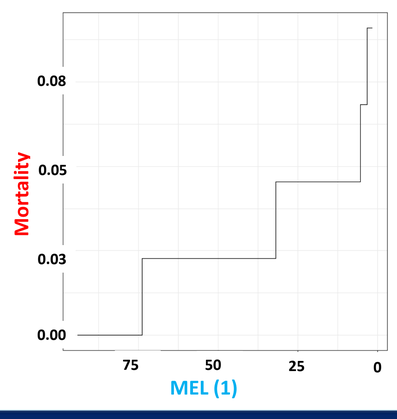
The correlation between the concentration of biomarkers and mortality was also evaluated. The increased mortality of patients with AIS was observed for the concentration of carbonyl groups determined < 4.5 h and within 1 day after exceeding the value of 250 U/mL and 350 U/mL, respectively. In the case of measuring carbonyl groups after 7 days, the increase in mortality is not so rapid as in the case of previous measurements, which may be related to the sample size considered in the study.
The rise in mortality was also seen for MEL levels measured < 4.5 h, during 24 h and on the 7th day (< 10 pg/mL determined < 4.5 h and within 24 h; < 15 pg/mL determined on the 7th day).

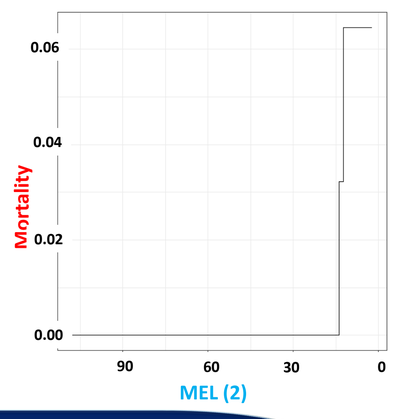












The results of the study demonstrated that the concentration of carbonyl groups was higher in patients with ischemic stroke (AIS) compared to the group of healthy people, which had an impact on the patients' prognosis. A lower concentration of the melatonin metabolite was also shown in the urine of patients, which suggests that patients treated with thrombolysis have low antioxidant protection. The determination of carbonyl groups at different time intervals may be an important potential parameter of protein damage in thrombolytic patients with AIS. Due to the neuroprotective effects of melatonin, attention should also be paid to the design and conduct of clinical trials, hormone supplementation in AIS patients, to understand the interactions between exogenous melatonin and its endogenous rhythm and how these relationships may affect patient outcomes.