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Effect of Therapeutic Hypothermia on Liver Enzymes in Patients With Stroke

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ABSTRACT

Introduction: A promising strategy that can lead to longer brain cell survival after an acute stroke is therapeutic hypothermia. It represents a controlled decrease in body temperature for therapeutic reasons. It is increasingly represented as a therapeutic option and is one of the most challenging treatments that improves neurological recovery and treatment outcome in patients with acute stroke. **Aim:** To examine the effect of therapeutic hypothermia on liver enzymes in patients with diagnosis of stroke. **Methods:** A total of 101 patients diagnosed with acute stroke were treated. The first group (n=40) were treated with conventional treatment and therapeutic hypothermia, while the second group (n=61) only with conventional treatment. Cooling of the body to a target body temperature of 34°C to 35°C was performed for up to 24 hours. Outcome (survival or death) of treatment was monitored, degree of disability was determined by National Institutes of Health Stroke Scale (NIHSS) and assessment of consciousness using the Glasgow Coma Scale (GCS). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values were taken at admission, after 24 hours, and were monitored upon discharge. **Results:** There was a significant difference in AST values at admission relative to disease outcome ($p = 0.002$), as well as for ALT ($p = 0.008$). In patients treated with therapeutic hypothermia, mean AST values decreased after 24 hours (32.50 to 31.00 IU/mL) as well as ALT values (27.50 to 26.50 IU/mL), without statistical significance. In the group of subjects who survived with sequela, AST values correlated with GCS (rho = -0.489; $p = 0.002$) and NIHSS (rho = 0.492; $p = 0.003$), ALT values correlated with GCS (rho = -0.356; $p = 0.03$) but not with NIHSS. **Conclusion:** AST and ALT values at admission correlate with the severity of the clinical picture. Therapeutic hypothermia is hepatoprotective and lowers AST and ALT values.

Keywords: brain, metabolism, therapy.

1. INTRODUCTION

A promising strategy that can lead to longer brain cell survival after an acute stroke is therapeutic hypothermia (1). It represents a controlled decrease in body temperature for therapeutic reasons (1). It is increasingly represented as a therapeutic option and is one of the most challenging treatments that improves neurological recovery and treatment outcome in patients with acute stroke (2). In animal models with ischemic stroke, a benefit in reducing infarct size and improved neurological outcomes has been demonstrated, while better outcome has also been demonstrated in patients with hypoxic-ischemic brain injury after cardiac arrest, with a potent neuroprotectant mechanism (2, 3, 4, 5). Although it represents a big step forward in stroke treatment, several clinical trials failed to prove the benefit of therapeutic hypothermia, presumably due to inadequate revascularization, with a slightly increased rate of pneumonia (4, 5, 6). Decreased body temperature reduces tissue metabolism and thus tissue oxygen demand (3, 7, 8). The resistance of sensitive tissues to hypoxia is increased by lowering body temperature, so cells can be preserved for a longer period in comparison to interruption of circulation at normal body temperature (1, 3). Neuroprotection is an essential therapeutic strategy in acute stroke (1, 3). Therapeutic hypothermia delays and slows neuronal damage, increases tissue tolerance to hypoxia, prevents brain damage by inhibiting oxidative stress, inflammatory reactions, metabolic disorders and apoptosis, reduces blood-brain barrier permeability and cerebral edema, reduces excitatory neurotransmitter release and free radical production, reduces infarction area, reduces intracellular calcium entry and intracellular acidosis, suppresses the formation of oxygen free radicals, delays increase of extracellular potassium, delays microglia proliferation and reduces microglial interferon-beta and nitric oxide production (1, 4, 9). The question of the effect of therapeutic hypothermia on liver metabolism is raised, which is very important for the optimized therapeutic modality.

2. AIM

The aim of this study was to examine the effect of therapeutic hypothermia on liver enzymes in patients with diagnosis of stroke.

3. PATIENTS AND METHODS

Patients and study design

The research (randomized, prospective, descriptive-analytical, clinical-applied) was conducted on 101 patients, who were included in the study in the period from June 2018 to January 2020. The first group (n=40) was treated at the Clinic for Anesthesiology and Resuscitation, while second group (n=61) was treated at the Clinic of Neurology, Clinical Center University of Sarajevo. The first group of patients was treated with conventional treatment (acetylsalicylic acid, statins, beta blocker, ceftriaxon 2 grams per day) plus therapeutic hypothermia, while second group was treated only by conventional treatment. Criteria for inclusion of patients in the study were: age over 18 years, body weight 50-120 kilograms, confirmed acute stroke by computed tomography, the possibility of initiating hypothermia within 6 hours from the onset of symptoms, the possibility of initiating hypothermia 1.5 hours after inclusion of thrombolysis (if it was in therapy), The National Institutes of Health Stroke Scale (NIHSS) 6-26, The Glasgow Coma Scale (GCS) ≥ 5. Criteria for exclusion of patients from the study were: pregnancy and lactation, acute myocardial infarcton within three months, acute alcohol intoxication, sepsis, severe hepatic impairment, renal failure, severe respiratory distress, bradycardia (<40 bpm), ejection fraction of left ventricle (EFLV) below 40%, vasospastic disorders and existence of skin damage (inflammation, burns, ulcerations, rashes). Informed consent was obtained from patient or family member, while Ethical approval was obtained from Ethics Committee of the Clinical Center University of Sarajevo.

4. METHODS

Mild systemic hypothermia and cooling of the body to a target body temperature of 34°C to 35°C was performed for 12 to 24 hours, using an Arctic Sun Temperature Management System (Medivance, Inc. of Louisville, Colorado). Periods of hypothermia lasted up to a maximum of 24 hours. To accelerate the onset of hypothermia, cold infusion solutions (0.9% sodium chloride or Ringer lactate at a temperature of 4 °C to 12 °C) were administered immediately in first hour. Infusion solutions of 4 °C were given for the first 60 minutes for intubated patients and up to 12 °C for non-intubated patients. The integrity of the skin was checked in the places where the pads were placed, i.e. cooling pads especially in diabetics, adipose and patients with peripheral atherosclerosis. Small doses of opiates are given to prevent shivering. After cooling, heating began at a rate of 0.2 to 0.5˚C per hour, and the treatment phase ended when the patient was warmed up to 36 °C, and then all cooling systems are turned off. In all patients with stroke, regardless of type (ischemic or hemorrhagic stroke), the outcome of treatment was monitored, and the degree of disability was determined using the NIHSS and assessment of consciousness using the GCS. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values were taken at admission, control was done after 24 hours, and were monitored upon discharge.

Statistical analysis

The Kolmogorov-Smirnov test was used to determine the distribution of continuous variables. Parametric tests (paired and unpaired t-test) were used in data analysis. Variables that showed a statistically significant deviation from the normal distribution were represented by the median and interquartile range (25th-75th percentile), and for their comparison according to reference values, repeated measurements and nonparametric tests (Wilcoxon signed-rank test, the Friedman test) were used. Spearman correlation was used for correlation testing. All analyzes were evaluated at a level of statistical significance of $p<0.05$.

5. RESULTS

Research included 101 patients with acute stroke, of which 44 (43.56%) were male and 57 (56.44%) were female. Of the total number, 91 (90%) patients had ischemic, while 10 (10%) had hemorrhagic stroke. In addition to standard therapy, therapeutic hypothermia was used in 40 (39.60%) patients. There was no difference in the age of the patients between the two groups ($p = 0.44$; 70.5 ± 12.74 vs. 72.3 ± 10.37 years), nor in the gender structure (56.44% females; $p = 0.81$).

AST and ALT values were analyzed and there were no difference between the mean ALT values between the two groups of subjects ($p=0.23$), while a significant difference was present in the AST values ($p=0.007$). There was no significant difference in AST values at admission, after 24 hours, and at discharge, in patients who were treated ($p=0.81$), and who were not treated with hypothermia ($p=0.15$) (Table 1). There was no significant difference in ALT values at admission, after 24 hours, and at discharge, and in patients treated with hypothermia ($p=0.36$), and who were not treated ($p=0.80$) (Table 2). In patients treated with therapeutic hypothermia, mean AST values decreased after 24 hours (32.50 to 31.00 IU/mL; $p>0.05$) as well as ALT values (27.50 to 26.50 IU/mL; $p>0.05$). In the group of patients who were not treated with hypothermia mean AST values increased (22.00 to 52.00 IU/mL; $p> 0.05$), along with mean ALT values (23.00 to 52.00 IU/mL; $p>0.05$). There was a significant difference in AST values at admission relative to disease outcome (survived with sequela or died) ($p = 0.002$; 22.00 vs. 38.00). In addition, there was a significant difference in ALT values at admission relative to disease outcome (survived with sequela or died) ($p = 0.008$; 22.00 vs. 30.00). In the group of patients who survived with sequela, AST values correlated with GCS ($\rho = -0.489$; $p = 0.002$). The correlation was moderate-

				Percentile			Friedman (χ^2)
Hypothermia - No	Time	Min.	Max.	25th	50th (Median)	75th	p
AST (IU/mL)	Admission	7.00	125.00	18,50	22,00	34,50	0,158
	After 24 hours	37.00	83.00	37,00	52,00	83,00	
	On discharge	15.00	69	21,00	25,00	40,00	
Hypothermia - Yes							
AST (IU/mL)	Admission	14.00	704.00	23,50	32,50	48,00	0,819
	After 24 hours	18.00	1181.00	22,00	31,00	66,00	
	On discharge	19.00	178.00	24,25	31,00	62,75	

Table 1. Aspartate aminotransferase (AST) values in subjects with acute stroke who and who were not treated with hypothermia on admission, after 24 hours and on discharge. IU/mL- International units per milliliter; Min. - minimum; Max. - maximum; p - level of significance.

				Percentile			Friedman (χ^2)
Hypothermia - No	Time	Min.	Max.	25th	50th (Median)	75th	p
ALT (IU/mL)	Admission	6.00	95.00	19.00	23.00	33.00	0.801
	After 24 hours	18.00	77.00	18.00	52.00	77.00	
	On discharge	14.00	132.00	15.00	28.00	43.00	
Hypothermia - Yes							
ALT (IU/mL)	Admission	8.00	1061.00	18.50	27.50	43.50	0.366
	After 24 hours	2.00	1445.00	15.75	26.50	31.75	
	On discharge	10.00	406.00	21.00	23.00	57.00	

Table 2. Alanine aminotransferase (ALT) values in subjects with acute stroke who and who were not treated with hypothermia on admission, after 24 hours and on discharge. IU/mL- International units per milliliter; Min. - minimum; Max. - maximum; p - level of significance.

ly strong and negative: higher AST values were found in subjects with lower GCS. AST is also correlated with NIHSS (rho = 0.492; p = 0.003). The correlation was moderately strong and positive: higher values of AST on admission were present in subjects with higher NIHSS. ALT values correlated with GCS (rho = -0.356; p = 0.03), the correlation is mild and negative, higher ALT values were found in patients with lower GCS. ALT values did not correlate with the NIHSS score (p = 0.55). In the group of subjects who died, AST and ALT values on admission were not in correlation with GCS and NIHSS (p> 0.05).

6. DISCUSSION

The question of optimal temperature for therapeutic hypothermia is still under investigation. Hypothermia can be defined as mild (>32°C), moderate (28–32°C), deep (20–28°C), profound (5–20°C), and ultraprofound (<5°C) (10). After cardiac arrest, the target temperature is 32–34°C, and the issue of target temperature for neuroprotection itself is still dubious (10). In this research, a temperature of 34°C to 35°C was used. Kollmar et al. on the 84 rat model of focal cerebral ischemia showed a neuroprotective effect at 33°C and at 34°C (11). Schwab et al. on 25 patients with ischemic stroke have demonstrated the safety of the use of hypothermia at 33°C (12). Krieger et al. published a pilot phase of The Cooling for Acute Ischemic Brain Damage (COOL AID) study involving 10 patients, suggesting that therapeutic hypothermia at 32±1°C is a safe method in patients with acute ischemic stroke even after thrombolysis (13). The Intravascular Cooling in the Treatment of Stroke (ICTuS) trial included 18 patients, who were underwent therapeutic hypothermia at 33 °C, and the trial substantially demonstrated the safety of the methods (14). Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS-L) trial also used a temperature of 33°C, and also showed the safety of the method, although an increased rate of pneumonia was recorded but not significantly related to outcome (15). Hong et al. used temperatures of 34.5° C in 39 patients, and demonstrated that therapeutic hypothermia may reduce the risk of cerebral edema and hemorrhagic transformation in patients undergoing recanalization after stroke (16). European multicenter, randomized, phase III clinical trial of therapeutic hypothermia plus best medical treatment vs. best medical treatment alone for acute ischemic stroke (EuroHYP-1) trial used a temperature of 34°C - 35°C on 1500 patients, started within six-hours of symptom onset and maintained for 24 hours and proved the benefit of the method itself (17). The Reperfusion and Cooling in Cerebral Acute Ischemia (ReCCLAIM) trial performed immediate cooling to 33 °C in 73 patients, and proved safety and feasibility of hypothermia in a unique cohort of patients following definitive reperfusion with endovascular approaches (18).

This research focused on liver enzymes, given the effect on the systemic metabolism of therapeutic hypothermia. On the other hand, this issue is very important for the optimized therapeutic modality, which is necessary in order to avoid liver failure.

Higher AST and ALT values at admission correlate with the occurrence of in-hospital mortality. This indicated that the values of AST and ALT should be taken into account when admitting the patient. In patients who survived, AST values correlated with lower GCS values and higher NIHSS values, which mean that patients with higher AST values represent patients with a severe clinical picture. ALT values correlate only with lower GCS. In the group of subjects who died, AST and ALT values did not correlate with GCS and NIHHS. These results suggest safety of therapeutic hypothermia, and that it does not have a detrimental effect on liver metabolism. After 24 hours, there was a decrease in AST and ALT values, indicating an effect of therapeutic hypothermia on them. Stravitz and Larsen stated that the induction of therapeutic hypothermia at 32°C -35°C has a hepatoprotective effect, and that it represents an effective bridge before transplantation in patients with acute liver failure (19). Karvellas et al. on 97 patients with acute liver failure who underwent therapeutic hypothermia stated that it could benefit in younger patients but does not affect on 21-day survival (20). Muniraman and Clarke at 70 asphyxiated neonates demonstrated a significant decrease in ALT concentrations on day 3 of hospitalization (21). Research on a larger number of patients would further establish therapeutic hypothermia as a treatment modality for stroke patients, and non-randomization is one of the study limitations. These results indicated that therapeutic hypothermia has an effect on AST and ALT values, and that it represents a safe method and a method that can be used synergistically for other therapeutic treatments, without fear of pharmacological interactions and the risk of liver failure.

7. CONCLUSION

AST and ALT values at admission correlate with the severity of the clinical picture, while therapeutic hypothermia is a hepatoprotective, and lowers AST and ALT values.

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- **Financial support and sponsorship:** No specific funding was received for this study.
- **Conflict of interest:** None to declared.

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