The impact of neuroprotection on brain metabolism and cognitive function during carotid endarterectomy

Introduction: Neuroprotection is a strategy that works against the biochemical and molecular manifestations that lead to ischemic brain injury. The aim of neuroprotection is to protect the hypoperfused brain region through influence upon ischemic cascade and by reducing the progress of injurious reperfusion. The development of neuroprotection has been proceeding alongside a growing understanding of brain ischemia pathophysiology. In spite of the demonstrable effects of many agents in animal models, until now none of the tested neuroprotective agents have been shown to improve the outcome in a phase III clinical trial.

Objectives: Primary objective of this study was to evaluate the impact of neuroprotection, administered before carotid endarterectomy, on brain metabolism and cognitive function. The potential influence of metabolic changes within the brain on clinical outcome was assessed. The secondary objective was to assess the satisfaction of patients with the type of anesthesia administered (general or local) and to consider the preference for general or local anesthesia during similar operations in the future.

Methods: A total of 35 patients underwent carotid endarterectomy with prophylactic combine neuroprotection (Sendai cocktail: Manitol, Phenhydan, Solumedrol, Tokoferol; Cerebrolysin; fraction of inspired oxygen (FiO_2) =1, middle arterial pressure (MAP) = 100 mmHg, total intravenous anesthesia - TIVA). The influence of neuroprotection on the clinical outcome, brain metabolism (S100B, glycaemia, lactate, pH, jugular vein bulb oxygen saturation - $SvjO_2$), and cognitive function (MMSE - Mini mental state exam, event-related potential (ERPs) - P300, N100) was evaluated. Metabolic parameters were acquired from jugular bulb during operation just before vessel unclamping. There were 35 patients in the control group who where operated on under local anesthesia without any neuroprotection. The results from both groups of patients were compared and statistically analyzed.

Results: Postoperative NIHSS (National Institutes of Health Stroke Scale) did not change in any patients in either group. In the neuroprotection group there were significantly higher levels of S100B (median 0.117 vs. 0.088; $p<0.0182$), lactate

(median 1.92 vs. 1.020; $p<0.0006$), glycaemia (median 9.5 vs. 8.2; $p<0.0243$), and $SvjO_2$ (median 0.79 vs. 0.65; $p<0.0001$). A significant decrease in P300 amplitude in first postoperative measurement was detected in neuroprotection group ($p<0.0046$). A significant decrease in N100 amplitude was detected equal in both groups during the first postoperative measurement. A significant increase in time latency of N100 was observed in the control group ($p<0.0180$). All patients operated on under general anesthesia were satisfied with this type of anesthesia and all of them would prefer general anesthesia again. 91,4% of patients operated on under local anesthesia were satisfied with this type of anesthesia but only 71,4% of them would prefer local anesthesia again (28.6% would prefer general anesthesia). The difference in the preference of the type of anesthesia is significant ($p<0,0001$). No significant differences were observed in other evaluated parameters.

Conclusions: Neuroprotection administered before carotid endarterectomy influences some brain metabolism parameters, both positively and negatively, however without impact on the clinical outcome.

Clinical consequences and the future: The main reasons that may have caused the failure of past clinical trials of neuroprotection are: extended therapeutic window, heterogeneous population of stroke patients, low dose administration, inadequate endpoints, discrepancies on outcome assessments in experimental and clinical trials, irregular study design and inadequate statistical evaluation. The future of neuroprotection is seen in concentration on the subgroup with existing penumbra, the combination of neuroprotection and thrombolysis and in prophylactic neuroprotection. The unification of the design in experimental and clinical trials is the main prerequisite for potential success of the clinical testing.