

CEREBRAL MICRODIALYSIS: PERIOPERATIVE MONITORING AND TREATMENT OF SEVERE NEUROSURGICAL PATIENT

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SUMMARY – The early signs of brain ischemia are key indicators of secondary brain injury and their recognition on time can ultimately save life. Direct recording of cerebral ischemia is possible using the method of cerebral microdialysis (CM). This paper presents results of the five-year experience in applying this method at University Department of Neurosurgery, Sarajevo University Clinical Center in Sarajevo. In this observational prospective clinical study, the treatment and outcome of 51 patients with subarachnoid hemorrhage (SAH) and traumatic intracranial hemorrhage (tICH) undergoing neurosurgery and consequently treated conservatively at Neurosurgical Intensive Care Unit (NICU) were analyzed. All patients were followed up by unified monitoring at NICU and additionally by the CM method. Between December 2006 and September 2010, CM monitoring was performed in 51 patients: 18 patients with SAH and 33 patients with tICH. In all patients, samples were obtained on 367 occasions, yielding a total of 3314 samples for biochemical parameters (mean 64.98 *per* patient, range 42-114 samples). Positive correlation was found between glucose level and outcome at one-year follow up (when glucose level was lower, the patient Glasgow Outcome Scale (GOS) score was worse). The correlation coefficient for glycerol was negative ($r=-0.81$), and so was for the lactate/pyruvate ratio. There was a significant difference in patient outcome in favor of the group of patients monitored by use of CM in terms of poor and good outcome graded according to GOS score 12 months after the injury compared with the group of patients not monitored with CM ($P<0.028$). According to our experience, we believe that CM enables early initiation of appropriate therapeutic strategies to overcome cerebral ischemia and secondary brain damage, eventually leading to better patient outcome.

Key words: *Microdialysis; Brain injury; Subarachnoid hemorrhage; Intracranial hemorrhage, traumatic; Postoperative care*

Introduction

Trauma is the leading cause of death in the first four decades of life, with head injury being implicated

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in at least half the number of cases¹. Traumatic brain injury (TBI) is a brain insult that leads to temporary or permanent disruption of cognitive and physical functions. Head injury was significantly involved in half of all deaths resulting from trauma. Annual prevalence in Europe is 700,000 cases, with total cost of around 3 billion €².

Severe brain trauma is the leading cause of death among young people in Bosnia and Herzegovina^{3,4}.

(BiH). Cerebral ischemia and intracranial hypertension are the most important secondary events in patients who have experienced difficult traumatic brain damage or extensive aneurysmal subarachnoid hemorrhage (SAH)^{5,6}. Early signs of ischemia (insufficient oxygen and glucose delivery to the brain) are the key indicators and guidelines for the treatment and their timely recognition can ultimately save lives. Direct recording of cerebral ischemia is possible using the method of cerebral microdialysis (CM), which monitors the intrinsic brain biochemistry in real time. This method allows for early initiation of appropriate therapeutic strategies to overcome cerebral ischemia⁷.

After brain trauma, the fundamental processes occur at cellular level and culminate in cell death. These processes include the release of cytotoxic amounts of amino acids, glutamate and aspartate, the production of free radicals and postproduction of lactate and hydrogen ions. The final, common path of these processes is often the entry of calcium into the cell, resulting in cell swelling⁸. This leads to cytotoxic cerebral edema. Brain, enclosed in a rigid shell (skull), is exposed to increasing intracranial pressure (ICP) and reduction in cerebral perfusion pressure (CPP), with the development of cerebral ischemia, reduction of tissue oxygen and glucose delivery, switching to anaerobic glycolysis, damage to the cell wall and death of individual cells⁹⁻¹¹.

Cerebral microdialysis (CM)

Microdialysis is an important technique for monitoring the biochemistry of tissues and organs in the human body. It is minimally invasive and comparatively simple method to perform in daily practice

of neurosurgery. A thin microdialysis catheter, 0.6 mm in diameter, is introduced into the tissue (brain parenchyma). A specially designed microdialysis pump pushes the physiologically compatible solution through the catheter into the tissue around the catheter. Interstitial equilibrium under the influence of the incoming fluid by the diffusion mechanism provides confluence of the excess dissolved liquid in another channel of the catheter, and dialysate is then fed back into the microvials for collection. The contents are then analyzed on a computer using a special reagent for glycerol, pyruvate, lactate and glucose. The monitor then shows the level of these molecules in the interstitial fluid (equivalent concentration). In fact, their volumes show metabolic events in tissues, and thus directly and in real time, suggest further therapeutic steps to provide the best possible conditions for the survival and function of nerve cells^{5,12,13}.

Since January 2006, the University Department of Neurosurgery in Sarajevo, as the first in southeastern Europe, uses the method of CM as a modality for recording tissue biochemical signs of cerebral ischemia in real time, and as a basis for therapeutic efficacy^{5,14}.

With the help of CM, the levels of glucose, glycerol, lactate, pyruvate and lactate/pyruvate (L/P) ratio in brain tissue in patients having suffered severe brain trauma and aneurysmal SAH are routinely monitored. The levels of glucose and L/P ratio are among the most sensitive and specific indicators of deterioration of cerebral metabolism during transient CPP decrease. Glycerol has been confirmed as an important indicator of ischemic neuronal damage, and its extracellular brain level is clearly associated with an advanced degree of ischemia^{15,16}.

Table 1. Therapeutic procedures in conservative and perioperative treatment of comatose neurosurgical patients (unselected and arranged in alphabetical order). These procedures are not in order of activity and are not explicit for each patient

Acid-base balance regulation	Constipation prevention	Neuroprotectors
Antihypertensives	DVT protection	Normoglycemia
Adequate oxygenation	Gastric mucosa protectors	Normotension
Antiedematous therapy	Hyperventilation	Nutritional support
Anticonvulsants	Hypothermia	Sedation
Balance of fluid intake and excretion	ICP control	Standard analgesia
Barbiturate coma	Inotropic agents	Steroids
Bed rest	Mineral correction	Triple H therapy (hypervolemia, hypertension, hemodilution)

Conservative treatment at NICU

Since the opening of the Neurosurgical Intensive Care Unit (NICU) in April 2003, a treatment protocol for neurotraumatized and SAH patients has been established^{14,17}. The protocol has been routinely used, with variations and general treatment plan modifications according to clinical presentation and findings in each individual patient. Decision on the type of treatment is made by the neurosurgeon in cooperation with the neuroanesthesiologist. Protocol implementation is in primary jurisdiction of a well-trained neuro-nurse, neurosurgical residents and anesthesiologists.

Based on clinical and neuroimaging features, treatment at NICU includes, depending on each individual case, different measures and methods (Table 1). Modern technological developments and collaborative approach of the neurosurgeon and neurointensivist to the neurotraumatized patient have significantly reduced the mortality of patients with TBI¹⁸. Despite these encouraging achievements in improving the treatment of patients with severe TBI and intracranial

bleeding lesions, there is still much room for improving the outcome (Figs. 1 and 2).

Multimodal neuromonitoring

There is evident increase in the use of multimodal monitoring in TBI patients. Due to low sensitivity of neurological examination of comatose patient, monitoring combined with perfusion imaging methods is a promising approach in the treatment of most difficult neurosurgical cases. Advanced monitoring techniques that provide information in real time (real-time monitoring), such as monitoring tissue oxygen saturation (PbtO₂), signal-processed EEG and neurochemical monitoring using CM are employed not only for early detection of secondary damage in the treatment of comatose patients, but can, as yet theoretically, be used as a basis and starting point for maintenance of the physiological environment of the injured brain¹⁸. Unlike traditional approach and reactive paradigm to take active neurosurgical intervention when the



Fig. 1. Three-dimensional MSCT (SSD technique) shows the skull of a study patient with extensive traumatic head injury. Note the complex multi-fragmental fractures, including skull base fracture, destruction of the orbital wall, frontal bone defect, and complicated fractures of the zygomatic bone, maxilla and mandible (fatal injuries).

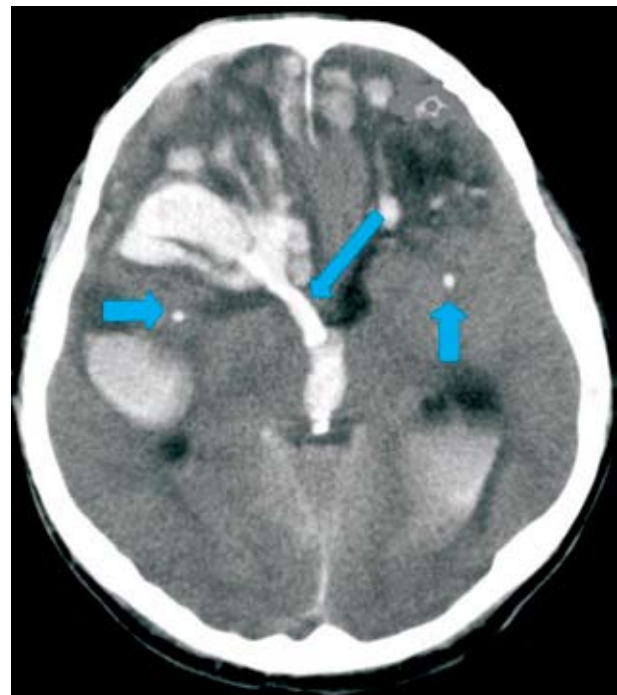


Fig. 2. CT scan shows extensive intracranial bleeding with multiple hemorrhagic focal contusions, penetration of blood into the ventricular system and mediosagittal structure shift. Both ICP (large arrow shows intraventricular catheter) and CM (short arrows show CM tip) were monitored, but no aggressive surgical intervention was performed.

harmful process is detected, goal-directed therapy based on microdialysis, continuous EEG and PbtO₂ promises proactive approach that can prevent secondary damage.

Patients and Methods

In this prospective clinical study, the treatment and outcome were analyzed in 51 patients with SAH and traumatic intracranial hemorrhage (tICH) treated operatively (neurosurgically) and then conservatively at NICU. The patients were followed up at NICU by unified monitoring and CM method. The study used CMA600 Microdialysis Analyzer, an apparatus for the collection and analysis of microdialysis findings (CMA Microdialysis, Sweden) and microdialysis CMA70 brain catheter. The ICU-pilot Software and LAB-pilot were used on data collection and processing.

CMA70 catheter has a diameter of 0.6 mm, with a membrane length of 10 mm, and is designed for intraparenchymal placement. The catheter was placed using the microinvasive microsurgical technique (intraoperatively) at one or two sites and in the 'worse zone' or penumbra zone and a 'better area', i.e. a zone

of normal brain metabolism (healthy, well-preserved parenchyma). The catheter has a gold tip that allows its visibility and location of the membrane on CT scan. The catheter has 2 branches at its extracerebral end. One, the input, is connected to the pump (CMA 106), which is fed continuously with Ringer solution through a catheter into the interstice, with the irrigation rate of 3 µL/min. The other branch is connected with a micro test tube, which is collecting dialysate sample.

Statistical analysis was performed using SPSS software Version 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

In this prospective randomized study, we conducted intensive postoperative neuromonitoring of patients with intracranial hemorrhage. From January 2006 to September 2010, CM monitoring was performed in 51 patients, 18 of them with SAH and 33 with tICH. In all patients, samples were obtained 367 times, yielding a total of 3314 samples for biochemical parameters (mean 64.98 *per* patient, range 42-114). Positive correlation was found between glucose and outcome at one year; as the glucose value was lower, the patient GOS score was worse (Mann-Whitney test). The correlation coefficient for glycerol was negative ($r=-0.81$, Spearman's Rank Correlation). Also, the correlation was negative for L/P ratio. There was a significant difference in patient outcome in favor of the group of patients monitored by use of CM (Kaplan-Meier method) in terms of poor and good outcome graded according to GOS score after 12 months of injury, as compared with patients monitored without the use of this method ($P<0.028$) (Figs. 3 and 4).

Discussion

It is widely accepted that CM can detect tissue damage and markers of cerebral ischemia, and can therefore be used to monitor biochemical changes caused by head injuries¹⁹⁻²³. Neuropathology of TBI is complex. Isolated brain monitoring of critically injured patients (TBI and SAH) only by use of CM, tissue oxygen saturation, continuous EEG, Doppler or other methods has not yet been generally accepted in terms of providing significant benefits for patients.

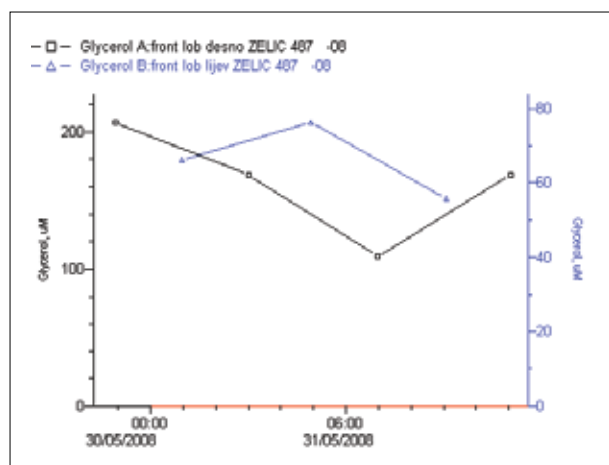


Fig. 3. Glycerol finding of the patient from Figure 2. Isolated CM record for the period of control recording. The chart was done by the ICU-pilot original software used in the study. As expected, in the left lobe glycerol values are moving to the basal values (50–80 mmol/L). In the right lobe, glycerol value after limited surgical intervention decreased from 220 to 120 mmol/L, but remained above the basal value, and started growing again soon thereafter.

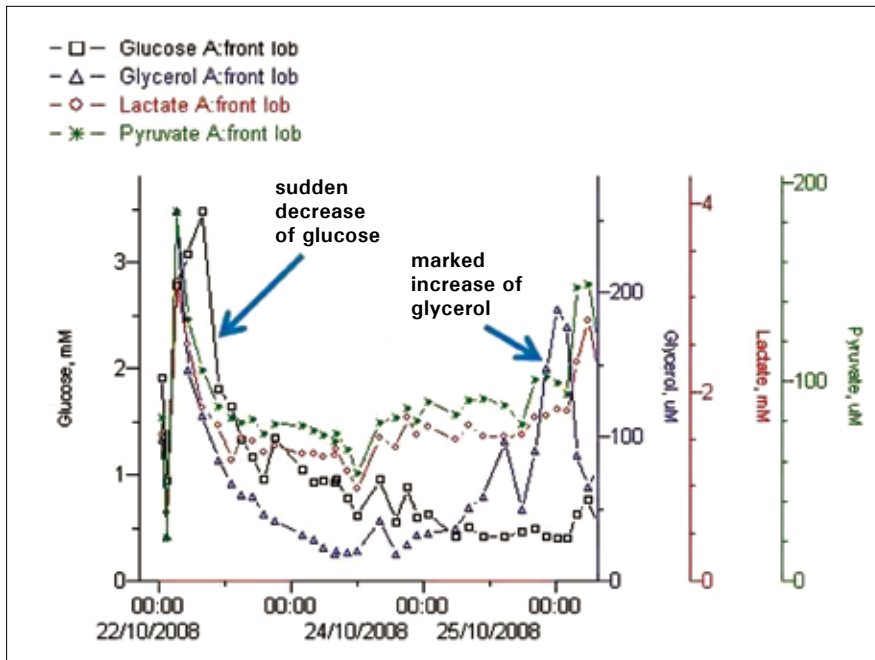


Fig. 4. Polygram showing microdialysis parameters of comatose patient in the first 7 days of treatment at NICU. There is an initial period of sudden depression of glucose level in the brain parenchyma (penumbra zone), below 1 mmol/L. After that, as a consequence of cell damage (cell wall), a marked increase of glycerol, above 180 µmol/L, is seen. At the time of rapid glucose decline, elevation of L/P ratio to 30 can be identified, with lactate concentration of 2.87 mmol/L and pyruvate concentration of 94 µmol/L (first postoperative day). The value of L/P ratio above 40 is considered as a significant sign of ischemia.

However, a combination of these methods, so-called multimodal monitoring, is almost a certain way to better outcome and there are ever fewer of those denying this fact or being skeptical. Wartenberg *et al.* have confirmed again earlier findings that human brain is almost entirely dependent on the uptake of glucose and its metabolites to maintain normal metabolism and function²⁴. Under normal aerobic conditions, glucose is metabolized into pyruvate, which generates large amounts of adenosine-triphosphate (ATP). During hypoxia or ischemia, anaerobic metabolism predominates, ATP production is much smaller, and the final product of glucose metabolism is lactate. All this leads to increased L/P ratio. Oddo *et al.* and Vespa *et al.* found the persistently low and decreasing levels of glucose in the brain to be associated with mortality and poor functional recovery of comatose patients^{25,26}. In our study, we found the patients showing deviation by about 25% of baseline threshold values in microdialysis findings for any of two or all three key markers (glucose, glycerol, and L/P ratio) for a period longer than 2 hours to have significantly deteriorated, as confirmed 7-19 hours later by neuroimaging.

Other indicators of secondary cell injury include increased brain concentrations of glutamate, an excitotoxic neurotransmitter, and of choline and glycerol, the final products of lipolysis, resulting in the ongoing destruction of the cell membrane.

As the neurosurgeon becomes more confident and free in the active management of these patients, not only in terms of surgery, but also in the pre- and postoperative period, and with independent decision making in neurointensive environment, the percentage of survival and better neurologic recovery is growing despite expectations based on earlier well-established and generally accepted postulates and predictions¹⁸. In the past, even in developed neurosurgical centers, and today in the centers without a standardized protocol, many neurosurgeons refused and/or are still refusing to treat extremely critical patients due to the demanding treatment and the expected poor outcome, or the treatment and full involvement of neurosurgeons refer only to selected cases. Nevertheless, many recent studies have shown that even patients with low grade can survive and recover well if treated aggressively from the start and properly monitored perioperatively^{5,13,18,27}. Monitoring changes in the brain under certain pathologic conditions require monitoring of global developments, but it is very much a situation where key changes occur at local level. On the other hand, some events require intermittent monitoring and as such are sufficient to assess the situation. In states where the events in the brain, in terms of secondary damage, are fast or very fast, there is the need for some kind of continuous monitoring. Cerebral microdialysis as a monitoring method provides partially contin-

uous but extremely frequent focal monitoring²⁸⁻³¹. In the postoperative period, advanced monitoring techniques such as continuous EEG, monitoring of brain tissue oxygenation and CM can detect hazardous and harmful secondary stroke and may thus be useful in targeted therapy in order to create optimal physiologic conditions of comatose patients with brain damage¹⁸.

In our study, we found the aggressive approach to a critical patient to be rational, while low Glasgow Coma Scale score at admission need not have always predicted poor outcome, although showing significant correlation.

According to the facts presented, it can be considered that we made a synthesis of fundamental neuroscience and microsurgery as well as practical and applicable skills that make one of the pillars of neurosurgery. Active neurosurgical operative treatment is not the end of the involvement of neurosurgeons in the treatment of patients, as is unfortunately sometimes the case, especially in general surgery centers. Neurosurgeon must be no less involved in perioperative monitoring, preparation and conservative treat-

ment of neurosurgical case with intracranial hemorrhage, as much as in the operative act itself.

Microdialysis technique is focused on perioperative monitoring and requires constant presence of neurosurgeons, and thus timely and meaningful intervention, i.e. contributing maximally to the outcome.

For all this, with our study we made an attempt to contribute to the association of basic research and clinical practice. Such reasoning and such a relationship with the clinician, basic science, in our conditions, mainly noticeable and unacceptable, are missing.

Further efforts in terms of ensuring better outcome of severe neurosurgical patients should be directed to:

- improving the efficiency of initial treatment and patient admission, and also improving the quality of neurosurgical operative treatment; and
- urge for the maximum feeling of responsibility of each physician and other medical personnel who come into contact with the patient, that every patient is equally important and equally “ours”, and to dedicate to the patient in the manner and according to their skill, training and responsibilities (Fig. 5).

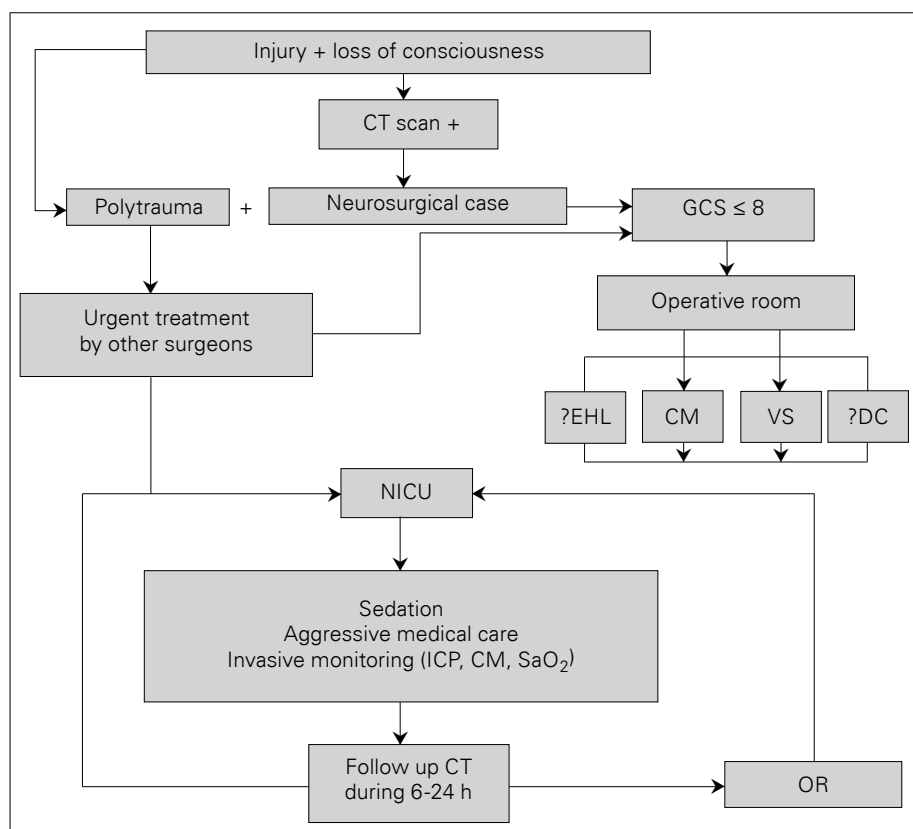


Fig. 5. Our (recommended) protocol for traumatized neurosurgical comatose patients, which implies ventriculostomy (VS) for ICP monitoring and placement of catheters for CM monitoring. Evacuation of hemorrhagic lesion (EHL) and decompressive craniectomy (DC) are conditional upon the choice of clinical presentation and CT findings. Follow up CT scan within 24 hours is also recommended. The central role of Neurosurgical Intensive Care Unit and “aggressive” perioperative treatment are emphasized.

Conclusion

Difficult patients need monitoring of intracranial pressure and cerebral perfusion pressure. Monitoring with cerebral microdialysis is also highly suggestible. Cerebral microdialysis, combined with other methods of neuromonitoring, can help in choosing target therapy for secondary stroke prevention. Adherence to protocols, standards and guidelines for the treatment of difficult neurosurgical trauma cases should be the obligation rather than choice. Complementary studies are welcome.

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Sažetak

CEREBRALNA MIKRODIJALIZA: PERIOPERACIJSKO PRAĆENJE I LIJEČENJE TEŠKOG NEUROKIRURŠKOG BOLESNIKA

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Rani znaci ishemijske mozga su ključni pokazatelji sekundarnih moždanih oštećenja i njihovo prepoznavanje na vrijeme može u konačnici spasiti život. Izravna registracija moždane ishemijske moguća je metodom cerebralne mikrodijalize (CM). U radu su prikazani rezultati petogodišnjeg iskustva u primjeni ove metode na Klinici za neurokirurgiju Kliničkog centra Univerziteta u Sarajevu. U prospektivnoj opservacijskoj kliničkoj studiji pratilo se liječenje i ishod u 51 bolesnika sa subarahnoidnim krvarenjem (SAH) i traumatskim intrakranijskim krvarenjem (tICH) koji su bili podvrgnuti neurokirurškoj operaciji, a potom konzervativno liječeni u Neurokirurškoj jedinici intenzivnog liječenja (NICU). Kod svih bolesnika je provedeno standardno praćenje u NICU i dodatno su praćeni metodom CM. U razdoblju od prosinca 2006. do rujna 2010. praćenje pomoću CM provedeno je u 51 bolesnika: 18 bolesnika sa SAH i 33 bolesnika sa tICH. U svih bolesnika uzorci su uzeti 367 puta, ukupno 3314 uzoraka biokemijskih parametara (prosječno 64,98 po bolesniku, raspon 42-114). Nađena je pozitivna korelacija između razine glukoze i ishoda u bolesnika nakon godinu dana praćenja; kada je razina glukoze bila niža, zbir GOS (Glasgow Outcome Scale) bolesnika bio je lošiji. Za glicerol je koeficijent korelacije bio negativan ($r = -0,81$). Negativna korelacija zabilježena je također za omjer laktat/piruvat. Postojala je značajna razlika u ishodu bolesnika u korist skupine bolesnika koji su praćeni pomoću CM u smislu lošeg i dobrog ishoda, prema zbiru GOS, 12 mjeseci nakon ozljede, u usporedbi s rezultatima bolesnika koji nisu praćeni pomoću CM ($P < 0,028$). Prema dosadašnjem iskustvu, vjerujemo da CM omogućava rano pokretanje odgovarajućih terapijskih strategija za prevladavanje cerebralne ishemijske i sekundarnih oštećenja mozga, što konačno vodi boljem ishodu bolesnika.

Ključne riječi: Mikrodijaliza; Moždana ozljeda; Subarahnoidno krvarenje; Intrakranijsko krvarenje, traumatsko; Poslijeoperacijska skrb