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CLINICAL STUDY

Mild hypothermia for intracranial aneurysm surgery

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Abstract: *Background:* Eighty nine patients with established intracranial aneurysm (Hunt-Hess score 1 to 3), who were operated at The Department of Neurosurgery, University Hospital Brno in 2003–2006, were enrolled in to the study group.
Methods: After introduction of anesthesia, we started cooling with two circulating-water mattresses (Blanketrol III, Cincinnatti Sub Zero). Body temperature was maintained at 34 °C during preparation of cerebral vessels. Active rewarming was started after clip putting. Cooling rate was 0.9±0.3 °C per hour and rewarming rate was 0.7±0.3 °C per hour. The required core body temperature was achieved in all patients, i.e. in 100 % of cases. Measured values of both esophageal and bladder temperature were not significantly different (p=0.4475). No significant difference was found when preoperative coagulation parameters and values measured during managed hypothermia were compared. Neurological condition was evaluated as good in 82 patients (92 %). Two patients died and one patient was in vegetative status.
Conclusion: When compared with similar group of patients, who underwent surgery in 1998 to 2002, where good treatment results were achieved in 80 %, final good neurological treatment results increased statistically significantly by 12 % due to managed hypothermia as well (p=0.0086) *(Tab. 4, Ref. 11).* Full Text (Free, PDF) www.bmj.sk.
Key words: intracranial aneurysm surgery, mild hypothermia, anesthesia management.

Efficiency of managed hypothermia as a perioperative neuroprotective method in clinical practice was not clearly proved. Clinical trials show that the lowest safe body temperature without any cardiovascular, metabolic and neurological toxicity is 33 to 35 °C. Consistent with our experience with administration of managed hypothermia in patients with brain injury, we decided to use this method perioperatively for patients undergoing neurosurgical procedure on cerebral vessels that are compromised potentially by ischemia most.

Neuroprotective methods are preventive therapeutic measurements for improving treatment neurological outcome in patients, who are at risk of cerebral ischemia formation. Primary effort is the prevention of damaging results of ischemia. While a lot of pharmacological agents were used for reducing of results of cerebral tissue damage, based on biochemical research and experimental trials, they did not prove very useful in clinical practice too much. Managed hypothermia is one of the effective methods for reducing of ischemia results, both in experiment and clinical practice. Mild hypothermia was clearly shown to improve ischemic neuronal damage results, while mild hyperthermia impairs these results (1). Multifactorial effect of hypothermia probably causes effect of hypothermia (2). Experimental studies confirm its effect on tissue homeostasis preservation by reducing of metabolism, limited release of excitatory amino acids, free radicals, and inhibition of cytoskeletal axonal damage after craniocerebral injury (3, 4). Neuroprotective effect of hypothermia in ischemic insult caused by circulatory arrest is also proven (5).

The aim of our study was to verify the potential of our anesthesiology method in combination with two circulating watery mattresses (Blanketrol III, Cincinnatti Sub Zero) technique to achieve required core body temperature measured in bladder and evaluation of influence of mild preoperative hypothermia on coagulation system. Finally, we compared current results of intracranial aneurysm surgical treatment were compared with results from the previous period, where managed hypothermia was not used as a neuroprotective method.

Materials and methods

After the approval of both Ethics Committees of our hospital and Ministry of Health of the Czech Republic, 89 patients with established intracranial aneurysm (Hunt-Hess score 1 to 3), who underwent surgery treatment in the Department of Neurosurgery, University Hospital Brno during 2003 to 2006, were enrolled in to the study group. Thirty five patients were treated for hypertension and 2 of them had also coronary artery disease with a history of myocardial infarction and they were classified as Hunt-

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Hess Grade 3 after suffering offrom subarachnoidal hemorrhage. From the anesthesiology point of view, the patients were in high risk for general anesthesia and surgery (classification ASA 4). All patients were operated within 48 hours after subarachnoidal hemorrhage onset. After evaluation of preoperative examination, the patients were premedicated in the evening with diazepam 10 mg orally and both atropine 0.5 mg and promethazine 50 mg were administrated intramuscularyly 45 minutes before the transportation to the surgery operating room. The patients with managed ventilation, who had already intubated trachea, were not premedicated. Intravenous bolus of midazolam 5 mg, fentanyl 0.1 mg and pancuronium 8 mg was administrated to these patients for undisturbed transport to the operating room. All patients were operated in air-conditioned operating room with temperature set at 24 °C.

After preoxygenation and intravenous administration of mesocain 100 mg, the patients were introduced to the general anesthesia by thiopental 5 mg/kg, midazolam 10 mg and fentanyl 0.1 mg. Cisatracurium 0.15 mg/kg followed by continuous infusion 1 to 2 μg/kg/min was used for muscle relaxation. After careful trachea intubation, artificial pulmonary ventilation was started with parameters keeping normocapnia. Infusion of manitol 0.5 mg/kg was also administrated to all patients. General anesthesia was further taken with sevoflurane 1 % in mixture of O_2 and NO_2 in ratio 1:1 with low gas input use during fentanyl administration.

Besides two peripheral intravenous cannules with sufficient lumen three-way central venous catheter through the right subclavian vein and another cannula to radial artery for invasive blood pressure measurement were introduced. Pulse oxymetry, capnography and diuresis measurement were obviously assessed as well. The catheter for jugular oxymetry measurement was introduced through the right jugular vein (monitor Vigilance, manufacturer Edward Lifesciences). $SvjO_2$ values were recorded from continuous measurement in 60 minutes interval. The core body temperature was measured in all patients by esophageal thermometer (Siemens) and by urinary catheter with temperature sensor (Kendall). Compared values of obtained core body temperatures were recorded in 60 minutes interval.

After introduction to anesthesia, cooling with two circulating-water mattresses placed below and on the patient was started (Blanketrol III, Cincinnatti Sub Zero). The temperature of the mattresses was set at 15 °C. Active cooling was interrupted after temperature of 35 °C was achieved. Following spontaneous temperature decrease, the a temperature of 34 °C was maintained during microsurgical manipulation on brain vessels. After finishing of aneurysm preparation and putting of a clip, active warming was started with the temperature of watery mattresses set at 40 °C.

Clonidin 1.5 g/kg was fractionally administered to all patients, because of hemodynamic stability securing and managed hypotense required by neurosurgeon during aneurysm preparation. In practice, decrease of systolic blood pressure to 80 to 90 mmHg is used by standard procedure with intravenous hypotensive drug that hat as shortest half-time as possible. The ideal drug for this purpose is sodium nitroprusside that was also used in our patients.

Fluids were administered in introductory phase of surgery in ratio 1:1 because of diuresis; after clipping we tried to restore intravascular volume and establish normotension by infusion of crystalloid or colloid solutions. Blood samples for hematology assessments were taken when the lowest temperature was achieved, at the time of start of active rewarming. All reported values are means ± standard deviation. Statistical evaluation was done by paired t-test. p-value <0.05 was considered statistically significant.

In patients in a good preoperative condition we tried to take out anesthesia and trachea extubation at the operating room and in patients observed and with managed preoperative ventilation we continued in artificial pulmonary ventilation also in early postoperative period. The surgery result was evaluated based on patient's condition within 6 months after surgery. Neurological condition was evaluated as good, if the patient returned to his/her original activities, or if he/she had a mild neurological and/or psychological deficit, but was able to take care of himself/herself. Neurological condition was evaluated as poor, if the patient died or he/she was in a vegetative status.

Results

Mean anesthesia time was 342±43 minutes, and mean surgery time was 268±26 minutes. Blood loss was 410±120 ml and perioperative measured diuresis was 1260±160 ml. Fluid intake was 3100±340 ml.

Core body temperature during introduction to anesthesia was 37.0±0.4 °C and the lowest core body temperature during surgery was 33.8±0.5 °C. The core body temperature when the patient was leaving the operating room was 35.9±0.5 °C. These values were recorded by the thermometer inserted to the bladder. The bladder is considered as the most suitable part for determination of brain temperature – for details see section Discussion. Mild hypothermia did not extend the time for taking out from anesthesia and extubation of our patients. The required core body temperature was achieved in all patients, i.e. in 100 % of cases. Measured values are shown in the Tables 1–4.

The temporary clip during surgery was used in 22 patients. Clipping time was between 4 and 9 minutes and in one case the temporary clip was inserted for 12 minutes. The final neurological condition was evaluated as good in this patient as well. Neu-

Tab. 1. Demographic data and localization of aneurysms.

Age	46±12
Gender (males/females)	47/42
Mean body weight (kg)	77±16
Localization of aneurysms	
– anterior communicant complex	42
– branching of the middle cerebral artery	18
– carotid area	13
– branching of the posterior communicant	7
– other	9

Tab. 2. Measured core body temperatures.

Time (minutes)	BT esophagus (°C)	BT bladder (±C)
0	36.7±0.5	37.1±0.4
60	35.9±0.3	36.2±0.4
120	34.8±0.3	35.2±0.3
180	34.0±0.4	34.3±0.3
Lowest BT	33.6±0.5	33.8±0.4
60	34.3±0.4	34.3±0.4
120	35.0±0.4	35.1±0.3
180	35.7±0.5	35.8±0.4

BT – body temperature

Tab. 3. Results of hematological tests.

	Preoperative	At the lowest BT
Leucocytes	8.8±2.2	10.5±3
Erythrocytes	4.7±0.5	4.3±0.4
Hemoglobin	145±14	133±17
Hematocrit	0.42±0.04	0.38±0.05
Platelets	202±36	207±33
INR	1.0±0.1	1.1±0.1
APTT	29±3	34±4
Thrombin time	17±2	16±3
Fibrinogen	3.7±0.4	3.4±0.5

INR – international normaliyed ratio, APTT – activated partial thromboplastin time

Tab. 4. $SvjO_2$ values (mean values measured in 50 patients).

Time (minutes)	$SvjO_2$ (%)
0	73±2
60	74±3
120	73±3
180	74±4
Lowest BT	73±3
60	74±3
120	74±3
180	75±4

rological condition was evaluated as a good in 82 patients (92 %). Two patients died and one patient was in vegetative status.

No significant difference (p=0.4475) was found for statistical comparison of esophageal and bladder temperatures.

Mean platelet counts before surgery and during preoperative hypothermia were 208±39 and 209±36, respectively. No significant difference was found (p=0.9774).

Mean INR values before surgery and during preoperative hypothermia were 1.0±0.1 and 1.1±0.1, respectively. No significant difference was found (p=0.4251).

Mean APTT values before surgery and during preoperative hypothermia were 30±4 and 34.6±5, respectively. No significant difference was found (p=0.0762).

Discussion

Managed hypothermia is currently considered as the method providing brain tissue protection against ischemic injury sequalae during neurosurgical procedures. Our prospective study verified effectiveness of our technique of patient cooling and rewarming, as well as safety of mild hypothermia during neurosurgical operations.

Primary goal of the study was to verify options of our anesthesiology procedure combined with two circulating-water mattresses Blanketrol III (Cincinnatti Sub Zero) to achieve required body temperature changes during anesthesia and neurosurgical operation in patients operated for intracranial aneurysm that is not always a simple procedure. For example, 12 % of patients (all of them were obese) were not able to be cooled to the required level of hypothermia in the study conducted by Hindmann (6). Changes of body temperature are influenced mainly by surrounding temperature, cooling technique, patient's body habit and anesthesiology procedure. Surrounding air temperature was set by default at 24 °C in our study. It is of course possible to work at significantly lower temperature, as it eases cooling; however we did not have to use this procedure because of 100 % success rate in achieving ofthe required temperature range in our patients. Cooling rate in patients enrolled to the study was 0.9±0.3 °C per hour and rewarming rate was 0.7±0.3 °C per hour. Core body temperature was 35.9±0.5 °C after finish ofthe surgery. Mild hypothermia did not extend time to taking out patients from anesthesia.

We would like to highlight two drugs we used for anesthesia, that besides other effects, help to manage body temperature and required changes of it. Sevoflurane seems to be an optimal anesthetic agent for neurosurgical patients due to its hemodynamic stability, mild vasodilatory activity and easy management of its activity. Clonidine is α_2-agonist with antihypertensive, sedative and anxiolytic properties. The major physiological activity of clonidine represents activation of α_2-adrenergic receptors and inhibition of neurotransmitter norepinephrine release. This results in significant reduction of sympato-adrenal activity and ensures vegetative stability of patient during surgery and extubation. Clonidine has a low polarity and therefore crosses blood-brain barrier readily, where influences CNS function in a various manner – it has sedative, anxiolytic, antimanic, and analgesic properties and decreases body temperature. This drug also significantly reduces consumption of anesthetics through its central activity. Based on its activity to presynaptic receptors, clonidin reduces norepinephrine release from postganglial sympathetic neurons and consequently reduces peripheral vascular resistance and blood pressure. Respiratory system is influenced very minimally.

Second goal of our study was to find, which method is more suitable for core body temperature measurement – in a bladder (catheter with thermistor Kendall) or in an esophagus (Siemens). Currently it is possible to measure direct brain temperature, however this technique is always invasive and all institutions worldwide prefer to measure temperature at other body sites. Our original plan was to compare our measured values with directly measured brain temperature in selected patients, but financial reasons did not allow us to do it for the time being. Therefore we use Henker's paper, which compared rectal, bladder and brain temperatures (7). However, this was intraventricular measurement in patients with craniocerebral injury, i.e. without craniotomy, that results in brain temperature reduction and reduction of differences between core body and brain temperatures that will be described further. The measured brain temperature in this study was in average higher by 0.8 °C then bladder temperature and by 1 °C then rectal temperature. Similar results also published Rumana, who found rectal temperature lower by 1.1 °C than brain temperature (8). As the mean core body temperatures in bladder found in our study are in average higher by 0.2 °C and therefore very likely nearer to brain temperature, the bladder is more suitable place for brain temperature identifying than esophagus. The temperature measured in esophagus is also more easily influenced by external effects, such as incorrect thermometer placement and effect of inhaled gasses temperature during artificial pulmonary ventilation. However, use of urinary catheter with thermistor is much more expensive compared to esophageal probe, since urinary catheters are not allowed to be reused in more patients. Similarly, the above mentioned difference in found values was statistically insignificant; therefore esophageal temperature measurement should be in usual neuroanesthesiological practice possible.

Safety of mild hypothermia in terms of coagulation system was already verified in patients with brain injury, where temperature decrease lasts is much longer then in patients undergoing operation for intracranial aneurysm (9). This study also did not find statistically significant changes when preoperative values in normothermia and preoperative results of coagulation parameters at the temperature 33.8 °C were compared. Mean blood loss 410±120 ml also corresponds to commonly published results and no increase compared to patients operated earlier in The Department of Neurosurgery without managed hypothermia use was observed.

Monitoring by jugular oxymetry during surgeries on cerebral vessels may be beneficiary and is globally recommended, as it can predict global reduction of cerebral metabolism, mainly when temporary clip is used. This decrease is relatively frequent in intracranial aneurysms clipping – up to 20 % of cases. No significant variations in $SvjO_2$ were recorded in our measurements.

In 2005 were publicated results of large-scale randomized trial of Todd and colleagues were published. At the final follow-up, 329 of 499 patients in the hypothermia group had a Glasgow Outcome Score of 1 (good outcome), as compared with 314 of 501 patients in the normothermia group (66 percent vs 63 percent). Authors demonstrated that intraoperative cooling has no overall benefit in this group of neurosurgical patients (10).

Despite this conclusion we think there are still reasons for perioperative use of controlled hypothermia in patients operated for intracranial aneurysm. Besides the results of plenty of experimental studies we have currently also clinical conclusions confirming the effectiveness of neuroprotective action of controlled hypothermia (5). Consequently the therapeutic hypothermia hads been enrolled into the guidelines for patients threatened by cerebral hypoxia after cardiac arrest (11). Also it is good to realize that the outcome score was better in hypothermia group, but not statistically significant in the above mentioned study. It is also possible that Glasgow Outcome Score is not specific enough to pick up the neurological differences between the groups. At least, but not last we had no other cost effective neuroprotective agent with minimal side effects in this time.

We understand that a large-scale randomized trial is necessary for clear demonstration of managed hypothermia effectiveness in patients undergoing surgery for intracranial aneurysm and therefore this demonstration was not (and could not be) the main goal of our prospective study. Nevertheless, comparison of final neurological treatment results with the results coming from other studies is relevant. Final neurological condition was evaluated as good in 82 (92 %) of patients. Death in 2 patients and vegetative status in 1 patient wasere caused by poor preoperative condition associated with serious complicating heart illnesses in two patients (these patients were classified as Hunt-Hess Grade 3, degree of anesthesiology risk according to ASA 4) and by vasospasm in one case (classification 2). Compared to similar group of 94 patients with Hunt-Hess classification <3, who underwent surgery in The Department of Neurosurgery between 1998 and 2002, where good results were achieved in 75 (80 %) of patients, current final neurological treatment results were improved statistically significantly by 12 % (Mann Whitney Wilcoxon test, $p=0.0086$). Comparison with the results of international trials conducted in nineties was similar (6). Our results are the consequence of a complex attitude to this topic. Perioperative use of managed hypothermia was on top of establishing of specialized neurosurgical team and introducing of new diagnostic and microsurgical techniques that forms the new way of management of these diseases.

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