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Therapeutic hypothermia and neurological outcome after cardiac arrest

Terapijska hipotermija i neurološki ishod nakon srčanog zastoja

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Abstract

Introduction/Aim. The most important clinically relevant cause of global cerebral ischemia is cardiac arrest. Clinical studies showed a marked neuroprotective effect of mild hypothermia in resuscitation. The aim of this study was to evaluate the impact of mild hypothermia on neurological outcome and survival of the patients in coma, after cardiac arrest and return of spontaneous circulation. **Methods.** The prospective study was conducted on consecutive comatose patients admitted to our clinic after cardiac arrest and return of spontaneous circulation, between February 2005 and May 2009. The patients were divided into two groups: the patients treated with mild hypothermia and the patients treated conservatively. The intravascular in combination with external method of cooling or only external cooling was used during the first 24 hours, after which spontaneous rewarming started. The endpoints were survival rate and neurological outcome. The neurological outcome was observed with Cerebral Performance Category Scale (CPC). Follow-up was 30 days. **Results.** The study was conducted on 82 patients: 45 patients (age 57.93 ± 14.08 years, 77.8% male) were treated with hypothermia, and 37 patients (age 62.00 ± 9.60 years, 67.6% male) were treated conservatively. In the group treated with therapeutic hypothermia protocol, 21 (46.7%) patients had full neurological restitution (CPC 1), 3 (6.7%) patients had good neurologic outcome (CPC 2), 1 (2.2%) patient remained in coma and 20 (44.4%) patients finally died (CPC 5). In the normothermic group 7 (18.9%) patients had full neurological restitution (CPC 1), and 30 (81.1%) patients remained in coma and finally died (CPC 5). Between the two therapeutic groups there was statistically significant difference in frequencies of different neurologic outcome ($p = 0.006$), specially between the patients with CPC 1 and CPC 5 outcome ($p = 0.003$). In the group treated with mild hypothermia 23 (51.1%) patients survived, and in the normothermic group 30 (81.1%) patients died, while in the group of survived patients 23 (76.7%) were treated with mild hypothermia ($p = 0.003$). **Conclusion.** Mild therapeutic hypothermia applied after cardiac arrest improved neurological outcome and reduced mortality in the studied group of comatose survivors.

Key words:
heart arrest; hypothermia, induced; neurologic manifestations; treatment outcome; mortality.

Apstrakt

Uvod/Cilj. Dokazano je da se blaga hipotermija, primenjena nakon srčanog zastoja, koristi u sprečavanju cerebralnog oštećenja kako za vreme srčanog zastoja, tako i nakon uspostavljanja reperfuzije. Cilj ove studije bio je da se utvrdi uticaj blage hipotermije na neurološki ishod i preživljavanje bolesnika u komi posle srčanog zastoja i spontanog uspostavljanja cirkulacije. **Metode.** U prospektivnu studiju uključeni su konsekutivni bolesnici lečeni u našoj ustanovi od 2005. do 2009. godine, koji su bili u moždanoj komi nakon srčanog zastoja, a kod kojih je ponovo uspostavljena spontana cirkulacija. Bolesnici su bili podeljeni u dve grupe: oni koji su lečeni hipotermijom i oni koji nisu. Korišćen je intravaskularni način hlađenja u kombinaciji sa spoljašnjim ili samo spoljašnje hlađenje u toku 24 časa, nakon čega su spontano zagrevani. Tokom 30 dana praćeno je preživljavanje i neurološki status skalom *Cerebral Performance Category* (CPC). **Rezultati.** Od ukupno 82 bolesnika u komi, 45 (57,93 ± 14,08 godina, 77,8% mušaraca) lečeno je hipotermijom, a 37 (62 ± 9,6 godina, 67,6% muškaraca) nije. U grupi lečenih hipotermijom 21 (46,7%) bolesnik imao je potpun neurološki oporavak (CPC 1), 1 (2,2%) ostao je u komi (CPC 4), a 20 (44,4%) umrlo je nakon perioda provedenog u komi (CPC 5). U drugoj grupi, 7 (18,9%) bolesnika imalo je potpuni neurološki oporavak

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(CPC 1), a 30 (81,1%) umrlo je nakon perioda provedenog u komi (CPC 5). Između bolesnika lečenih hipotermijom i kontrolne grupe zabeležena je visoka statistički značajna razlika u neurološkom ishodu između grupa CPC 1 i 5 (p = 0,003). U grupi bolesnika lečenih hipotermijom, 23 (51,1%) je preživelo, dok je u kontrolnoj grupi umrlo njih 30 (81,1%) (p = 0,003). **Zaključak.** Blaga hipotermija dovela je do sniženja mortaliteta i poboljšanja neurološkog ishoda kod bolesnika u komi nakon srčanog zastoja.

Ključne reči:
srce, zastoj; hipotermija, izazvana hladnoćom; neurološke manifestacije; lečenje, ishod; mortalitet.

Introduction

Individually, the most significant clinically relevant cause of global cerebral ischemia is cardiac arrest. The frequency of cardiac arrest is estimated at 40 to 130 cases in 100,000 people per year [1, 2]. Unfortunately, a complete cerebral recovery is still rare. Almost 80% of the patients who experienced the return of spontaneous circulation remain comatose for more than one hour. One year after cardiac arrest only 10%–30% of patients survive with favourable neurological outcome [3]. Possibility for survival in patients with brain anoxia is dramatically increased by using protective and preservative hypothermia [4]. Therapeutic hypothermia has a long history as a treatment used for different purposes. Hippocrates recommended the use of cooling to stop bleeding. Fay used cooling of extremities in patients with tumors [5]. However, it was not until the 1950s, when effects of hypothermia on oxygen metabolism were studied more extensively, that hypothermia was used more often as a therapeutic method, especially in cardiac surgery. It was used for protection and preservation of the heart and the entire organism during the planned operative ischemia [6]. Soon afterwards, hypothermia was used in resuscitation after cardiac arrest and as a treatment of craniocerebral injuries. In the early 1990s it was found that mild hypothermia applied after cardiac arrest had beneficial effect on the brain protection; prevention of cerebral injury not only during arrest, but also after reperfusion. Similar results were obtained in craniocerebral injuries [5].

Peter Safar made a significant contribution to the application of hypothermia in resuscitation so it became an important segment in the chain of survival [5]. For this reason, the aim of our study was to evaluate the impact of mild hypothermia on neurological outcome and survival of the patients in coma after cardiac arrest and return of spontaneous circulation.

Methods

The conducted study was prospective, and included the patients treated in our Clinic in the period from February 2005 to May 2009. It included consecutive patients in coma, after out-of-hospital cardiac arrest, who experienced return of spontaneous circulation (ROSC). Cardiopulmocerebral resuscitation was conducted by doctors providing emergency medical service according to the protocol of advance life support (ALS). The patients were divided into two groups: those who had been treated with hypothermia and those who had not (the control group). The study included the patients able to receive therapeutic hypothermia within 240 minutes after spontaneous circulation having been restored. The study did not include patients with trauma and/or serious bleeding, terminal stage of the disease and/or pregnancy and/or coagulopathy, and the cases with more than 240 minutes after the return of spontaneous circulation. Cooling was performed according the International Liaison Committee on Resuscitation (ILCOR) protocol, which recommends that the body temperature of unconscious patients who experienced spontaneous return of circulation after cardiac arrest should be lowered to 32 to 34°C over a 12–24-hour period, when the initial rhythm was ventricular fibrillation. This manner of cooling is considered efficient in other disorders of heart rhythm leading to cardiac arrest [7]. The procedure applied was either intravascular cooling in combination with external cooling (38 patients) or external cooling (7 patients) with cooling pads (Emcools pads, Emergency cooling systems AG, Vienna, Austria). Through Swan-Ganz catheter placed in the pulmonary artery, infusions of cold saline (4°C) (physiological or Ringer's solution) were administered at dosage of 30 mL/kg at 100 mL/min. Ice packs were applied to body surface in the area of groin, chest, axilla, neck and head. Cooling lasted for 24 h, and after that the patients were spontaneously re-warmed. Analgosedation and myorelaxation were carried out on all the patients, and the patients were on invasive mechanical ventilation with intermittent positive pressure (IPPV Mod). The medicaments used in analgosedation are morphine sulphate 5 mg intravenously, midazolam 15 mg intravenously. Pancuronium 0.1 mg/kg was administered intravenously for myorelaxation. Continuous analgosedation was performed by intravenous infusion of propofol (600 mg). Continuous monitoring of temperature was performed using Swan-Ganz catheter placed in the pulmonary artery. When only external cooling was applied, the pads were placed on the chest, back and limbs. All the patients received invasive manner of measuring arterial pressure and hourly diuresis was monitored, as well. Parameters of pulmonary circulation pressure were checked as well as continuous ECG monitoring. Primary attention was paid to survival rate and neurological status of the patients. Cardiac status was checked by clinical examination, echocardiographically and invasively, using parameters of cardiac microcatheterisation, arterial pressure and coronary angiography [6]. Neurological status was observed by clinical examination and non-invasive diagnostic imaging techniques (CT and NMR), as well as Glasgow Coma Score (GCS) [8] and Cerebral Performance Category Scale (CPC) [9]. The patients were observed for 30 days.

Cerebral Performance Categories are:

– Favourable neurological outcome: the patient is conscious, able to work and have normal life; may have slight psychological or neurological deficit (mild dysphasia, mild hemiparesis, or minimal dysfunction of cranial nerves);

– Moderate cerebral injury: the patient is conscious, able to work part-time in certain environment, able to perform daily activities (getting dressed, using public transport, and preparing food). The patient may suffer from hemiplegia, ataxia, dysarthria, dysphagia or constant disorder of memory and mental status;

– Serious brain injury: the patient is conscious, needs assistance in performing daily activities. There is a wide range of brain function disorders including memory disorder, dementia, inability to communicate;

– Coma, vegetative state: the patient is not conscious;

– Death: Verified brain death or death verified by means of traditional criteria.

Parameters of descriptive statistics used in the study were arithmetic mean, standard deviation, and relative numbers. Analytical statistical methods applied to this study were the method of identification of empirical distributions and the method of evaluation of significant difference (*t*-test and χ^2 test).

Results

The study included 82 patients. Therapeutic hypothermia was applied to 45 patients, while 37 patients were not subjected to hypothermia. The average target temperature was 33.3°C. The most important characteristics of the patients at the beginning of the study are presented in Table 1.

After 30 days of observations, in the group of patients who were cooled, a total of 21 (46.7%) patients had good neurological outcome with CPC 1, three (6.7%) patients had almost completely good neurological outcome with CPC 2, one (2.2%) patient remained comatose with CPC 4, whereas 20 (44.4%) of the patients remained comatose and died with CPC 5. Out of all the patients who were not cooled, seven (18.9%) had completely good neurological outcome with CPC 1, whereas 30 (81.1%) patients remained comatose and finally died with CPC 5. Comparing the group of patients treated with hypothermia and the group of patients who were not treated with hypothermia, there was a high statistically significant difference in frequency of different neurological outcomes ($p = 0.006$), and between the CPC 1 and 5 ($p = 0.003$) (Table 2).

In the group with hypothermia 23 (51.1%) patients survived. In the group of normothermic patients seven (18.9%) patient survived, and 30 (81.1%) patients died. Comparing the total number of the patients who survived, 23 (76.7%) were in the group treated with hypothermia ($p = 0.003$) (Table 2).

The patients had no complications during the treatment with therapeutic hypothermia.

Table 1

Baseline characteristics of the patients included in the study

Characteristics	Hypothermia (n = 45)	Normothermia (n = 37)	*p*
Age (years), ($\bar{x} \pm SD$)	57.9 ± 14.08	62.0 ± 9.6	0.139
Gender [n (%)]			
male	35 (77.8)	25 (67.6)	0.299
female	10 (22.2)	12 (32.4)	
Ejection fraction < 35% [n (%)]	14 (32.6)	18 (48.6)	0.178
Ventricular fibrillation [n (%)]	27 (60)	19 (52.8)	0.693
Glasgow coma score < 7 [n (%)]	40 (88.9)	34 (91.9)	0.648
Time to ROSC*(min), ($\bar{x} \pm SD$)	26.9 ± 4.7	27.6 ± 3.6	0.467
Myocardial infarction [n (%)]	33 (73.3)	28 (75.7)	0.809

***ROSC – return of spontaneous circulation**

Table 2

Influence of therapeutic hypothermia on neurological outcome and mortality rate in patients with coma after cardiac arrest returning to spontaneous circulation

Parameters	Patients (%)	
	Hypothermia	Normothermia
Neurological outcome		
CPC 1	46.7	18.9†
CPC 2	6.7	–
CPC 3	–	–
CPC 4	2.2	–
CPC 5	44.4	81.1*, †
Mortality rate		
survived	51.1	18.9
died	48.9	81.1

CPC (Cerebral Performance Category Scale) – for explanation see Methods

***p* = 0.003 *vs* CPC 1 within the same group; †*p* = 0.006 *vs* corresponding CPC value in the patients with hypothermia**

Discussion

The results of clinical studies indicated a significant neuroprotective effect of mild hypothermia (32–34°C) applied in resuscitation [10, 11]. Our study indicates that 46.7% of the cooled patients had good neurological outcome and 51.1% of the patients survived, while 18.9% of the patients who were not treated with hypothermia survived and had a complete neurological recovery. The two largest and most important studies, on the basis of which resuscitative hypothermia was officially recommended for cardiopulmocerebral resuscitation, were published by Bernard et al. [11] and Hypothermia After Cardiac Arrest (HACA) Group [9] and included in the European Resuscitation Council Guidelines for Resuscitation 2005 [12]. Bernard et al. [12] published data indicating decrease in mortality rate and improvement of neurological outcome in patients with out-of-hospital cardiac arrest. In this study, cooling was performed in the field by Emergency Medical System team using ice packs. External cooling continued in hospital conditions. Twenty-one patients out of 43 in the examined group survived with good neurological outcome (49%), whereas in the control group 9 (26%) patients survived out of 34 with good neurological outcome. The difference was significant. Hypothermia caused lower cardiac index, increased systemic vascular resistance and hyperglicemia [12].

In the HACA study, 55% of the patients in the examined group had moderate neurological insufficiency or did not have, comparing to 39% in the control group. The difference is statistically significant [9]. During a 6-month period mortality rate was 41% in the hypothermic group comparing to 55% in the normothermic group. In the HACA study, the patients were cooled for more than 8 hours, until the target temperature of 33°C was reached, and it was maintained for the following 24 hours. After that, the patients were spontaneously rewarmed until normothermia [9, 13]. The process of cooling our patients lasted for 24 h, and after that the patients were spontaneously rewarmed. There are still no data based on large studies revealing the optimal period of maintaining mild hypothermia, whether it is 12, 24 or 48 h, but it is clear that the effect of mild hypothermia is more beneficial if the temperature between 32 and 34°C is reached sooner [14]. It is still necessary to wait for the results of large studies to prove what manner of cooling is the most optimal (external, combination of external and intravascular or intravascular) [14].

There are several possible mechanisms enabling mild hypothermia to improve neurological outcome after reperfusion. In the normal brain, hypothermia decreases cerebral usability of oxygen by 6% for each degree of decrease in brain temperature when body temperature is higher than 28°C [15]. Mild hypothermia is considered to block many chemical reactions associated with reperfusion injury. These reactions involve formation of free oxygen radicals, increased release of amino acids and disorder in intracellular calcium metabolism. All these reactions lead to the damage of mitochondria and apoptosis [15–17]. Despite its potentially beneficial effects, hypothermia may also cause negative side effects such as arrhythmia, infection and coagulopathy.

No negative side effects of this type of treatment were recorded in our study.

The best results of cooling are achieved when the initial rhythm is ventricular fibrillation. This was proven by Oddo et al. [18] whose study included 109 comatose patients after cardiac arrest with the initial rhythm of ventricular fibrillation. A favourable outcome was recorded in 56% of the patients who were cooled comparing to 26% of the patients who did not have satisfactory outcome and were not cooled. The difference was significant. The difference was not significant when the initial rhythm was pulseless electrical activity or asystole [18]. Similar results were obtained in "Cool it" study which included patients with acute myocardial infarction with ST segment elevation who suffered cardiac arrest and who remained comatose after ROSC [19]. Primary Percutaneous Coronary Intervention (pPCI) was performed in all the patients. The survival rate was significantly higher when the initial rhythm was ventricular tachycardia/ ventricular fibrillation, than in cases where the initial rhythm was pulseless electrical activity or asystole (73% *vs*. 39%). The difference was significant. Therapeutic hypothermia after cardiac arrest can be applied together with primary percutaneous coronary intervention in the treatment of acute myocardial infarction [6]. This was proven by Wolfrum et al. [20] whose study included 33 comatose patients after cardiac arrest with acute myocardial infarction with ST segment elevation. The initial rhythm was ventricular fibrillation. Primary percutaneous coronary intervention was performed in all these patients, and therapeutic hypothermia only in the study group. A tendency of lower mortality rate was found in the cooled patients (25% *vs*. 35%), as well as better neurological outcome with CPC 1 or 2 (69% *vs*. 47%).

Conclusion

In the examined group of patients in coma after cardiac arrest, induced mild therapeutic hypothermia decreases mortality rate and improves neurological outcome.

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