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THERAPEUTIC HYPOTHERMIA FOR ORGAN PROTECTION IN CRITICAL CARE

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ТЕРАПЕВТИЧЕСКАЯ ГИПОТЕРМИЯ ДЛЯ ЗАЩИТЫ ОРГАНОВ В КРИТИЧЕСКИХ СЛУЧАЯХ

В исследование были включены 58 больных с внутричерепными гематомами (n=44) и кардиогенным шоком (n=14), чтобы оценить эффективность терапевтической гипотермии (ТГ) в соответствии с изменениями системной и церебральной гемодинамики, что приводит к дисфункции органов.

Для мониторинга был использован широкий спектр методов и инструментов. Были обнаружены положительные эффекты ТГ, влияющие на периферический и мозговой кровоток. Инициирование ТГ привело к снижению постгипоксической энцефалопатии наравне с уменьшением признаков гипоперфузии внутренних органов. Кроме того, ТГ оказало положительное влияние на течение синдрома полиорганной недостаточности. Коэффициент смертности в группе ТГ незначительно снизился по сравнению с контрольной группой.

Массив соответствующих вопросов предлагается для дальнейших исследований. Инициирование неинвазивной ТГ не противоречит другим стратегиям ведения данных больных. В сочетании с другими методами интенсивной терапии ТГ является эффективным решением для защиты органов от вредного воздействия гипоксии. Однако инициирование ТГ, особенно у нейрохирургических больных, требует расширенного мониторинга. Терапевтическая гипотермия — высокоэффективная модель в интенсивной терапии нетравматических субарахноидальных кровоизлияний.

Ключевые слова: переохлаждение, интенсивная терапия, внутримозговые гематомы, кардиогенный шок.

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THERAPEUTIC HYPOTHERMIA FOR ORGAN PROTECTION IN CRITICAL CARE

58 patients with intracerebral hematomas (n=44) and cardiogenic shock (n=14) were included in the study to assess the effectiveness of therapeutic hypothermia (TH) according to the changes in systemic and cerebral hemodynamics, leading to organ dysfunction. A wide range of methods and tool were used for monitoring. Positive effects of TH on the peripheral and cerebral blood flow have been found. Moreover, the initiation of TH reduced post-hypoxic encephalopathy as well as the signs of hypoperfusion of splanhnic circulation. TH produced a positive effect on the course of multiple organ dysfunction syndrome. Mortality rate in the TH group slightly decreased compared to the control group. An array of relevant issues is proposed for further sudies. The initiation of non-invasive TH does not interfere with other management strategies. TH combined with other intensive care modalities appears to be an effective option for protecting organs against the deleterious

effects of hypoxia. The initiation of TH, particularly in neurosurgical patients, requires advanced monitoring. TH is a high effective modality in intensive care of nontraumatic subarachnoid hemorrhage.

Key words: hypothermia, critical care, intracerebral hematoma, cardiogenic shock.

Background

During the last decade hypothermia being a promising method for protecting organs against the deleterious effects of hypoxia has stepped over the threshold of the research laboratories and is in daily clinical practice (6; 7). Many studies concluded that hypothermia is a highly effective modality to prevent intraoperative brain injury with the further development of post-hypoxic encephalopathy caused by sudden cardiac arrest, neonatal hypoxic-ischemic encephalopathy, stroke, head and spinal cord trauma. This beneficial effect was evidenced also for cranial-cerebral hypothermia and therapeutic hypothermia (TH) (13; 14). Thus, the specific mechanisms of hypothermic protection remain unclear. It is assumed that TH interrupts or modulates metabolic, molecular and cellular pathways leading to neuronal death (8). Over the decades the prevention of multiple organ dysfunction syndrome (MODS) in critically ill patients remains relevant. Despite all innovations and improvements in organ protection, MODS is associated with 23–25 % mortality rate. Indeed, a new phenotype of MODS has emerged — persistent MODS (PICS — persistent inflammation, immunosuppression, and catabolism syndrome), characterized by prolonged stay in intensive care units (ICU), when organ dysfunction may be controlled, but not treated, and is accompanied by recurrent infections with mild systemic inflammatory response syndrome (SIRS), lymphopenia, and decreased lean mass (2; 17). We hypothesized that TH can prevent the development of MODS in critically ill patients. Therefore, the aim of the present study was to assess the effectiveness of TH in different groups of intensive care patients.

Material and Methods

A prospective, non-randomized study was approved by the Local Ethics Committees of the Research Institute for Complex Issues of Cardiovascular Diseases and Kemerovo Cardiology Dispensary. 58 patients underwent TH using an Arctic Sun 5000 Temperature Management System (BardMedical, USA) with the conductive pads placed on the chest and lower extremities of the patient. TH with the target temperature (T °) 34°C was induced at the time of admission to the ICU. The duration of TH was 52 hours (min 38, max 64). TH was performed in 44 neurosurgical patients with cerebral aneurysm rupture, complicated by subarachnoid hemorrhage, cerebral vasospasm (CV), cerebral edema, who had undergone craniotomy and aneurism clipping. TH was performed in 14 cardiac patients admitted to the ICU with cardiogenic shock who had undergone percutaneous coronary intervention (multivessel stenting and / or angioplasty). All cardiac patients were on intra-aortic balloon pump (IABP) combined with mechanical ventilation and inotropic support at high doses. The control group consisted of 20 patients (10 neurosurgical patients and 10 cardiac patients), who were comparable in clinical and anthropometric data. The exclusion criteria were as follows: standard contraindications for TH (3). In 20 patients (34.5 %) the full scope of monitored parameters was not achieved due to the absence of the need to place the intracranial pressure (ICP) sensors. Main clinical laboratory data were measured and analyzed. Jugular venous oxygen saturation (SbvjO2) was estimated from the lesion site in neurosurgical patients. Parameters of central hemodynamics were evaluated using a patient monitor Nihon Koheden ISM4113K, Japan with the calculation of delivery / oxygen consumption (DO_2 / VO_2). Intracranial pressure was measured using a Spiegelberg brain pressure monitor, Germany). Linear blood flow velocity (BFV) was measured using a transcranial Doppler monitor "Angiodin Universal" (BIOSS, Russia). Basal metabolic rate (BMR) was assessed using a monitor "MPR 6-03

Triton" (Triton, Russia). Regional perfusion was estimated using the resistive index (RI) in the mesenteric and renal arteries with a scanner «Vivid-7 Dimention», General Electric, USA). The severity of patients' illness was assessed using the SOFA score. Serum levels of biochemical prognostic markers of MODS (S100, intestinal fatty-acid-binding protein (I-FABP) were measured every 12 hours during TH treatment. Data are presented as median and 25th and 75th percentiles (Me [25 %, 75 %]). All statistical analyses were computed using "Statistica. 6.1."

Results and Discussion

Neurosurgical patients during TH treatment exhibited hyperdynamic type of hemodynamic profile due to hyperthermia (T° 37.8 [37.5; 38.6]), whereas in cardiac patients hyperdynamic type was associated with reperfusion and inotropic support. Initially elevated CI (7.4 [5.2; 8.6] l / min / m^2) decreased to subnormal values (-5.5 [3.6; 5.9] l/ min/m^2) after 4 hours of TH treatment (reaching moderate hypothermia 35.8 °C). When the target temperature was achieved, CI reached normal values (3.3 [2.9, 3.9] l/ min/m^2). The dosage of the inotropic support was not changed. Thus, tachysystole, 124 [112; 138] beats \ min decreased to subnormal values — 86 [68; 97] beats/min. Several studies reported (11; 15) the development of peripheral spasm in hypothermia below 35 °, but in our study initially elevated index of peripheral vascular resistance, 2384 [2019; 2645] dyn·s/(cm^5·m^2), remained within the normal range and was 1562 [1133; 1728] dyn·s/(cm^5·m^2) at the central T° 34.2. Peak systolic velocity in the middle cerebral artery decreased up to 30 % out of initial value (from 267 [212; 334] cm/sec to 162 [149; 190] cm/s) leading to decreased Lindegaard index. There were no changes observed during the rewarming. The above-mentioned tendency is reported by numerous studies (10; 12), and may be considered as a main mechanism of cerebral protection produced by TH.

Biochemical markers of brain tissue, S100 protein, also demonstrated a tendency to decrease up to normal values by the first day of TH treatment (Table 1). The obtained data are consistent with the results of other studies (1; 16; 18).

Changes observed in basal metabolic rate during TH treatment are presented in Table 2.

Minimum values of BMR were achieved by 36 hours after TH treatment and remained at the same level during rewarming. Few studies reported similar results (6, 13) as BMR is supposed to be rather volatile parameter, which depends on different factors, and, primarily, on the adequate and balanced nutrition.

Table 1

Levels of S100 during TH, ng / ml, Me [25%, 75%]

Parameters	Baseline	24 hours of TH	Rewarming
Reference values	0.5–17	0.5–17	0.5–17
TH group	21.6 [20.4; 28.8]	17.7 [7.7; 27.7]	12.9 [7.8; 25.6]

Table 2

Basal metabolic rate during TH, kcal, Me [25%, 75%]

Parameters	Baseline	12 hours of TH	24 hours of TH	36 hours of TH	Rewarming
Reference values	1900–2100	1900–2100	1900–2100	1900–2100	1900–2100
TH group	2766 [1998; 3010]	2120 [1960; 2990]	1990 [1240; 1999]	1240 [1017; 1870]	1240 [1010; 1890]

The rate of posthypoperfusion dysfunction decreased in the TH group. Thus, the rate of paralytic ileus and pancreatitis was significantly lower in the study group compared to the control group (40.9 % (18) vs. 80 % (8), respectively). Similarly, the rate of renal failure was lower in the study group, compared to the control group (11. 4 % (5) vs. 20 % (2), respectively) according to the RI (Table 3). Regional perfusion was characterized by an initial moderate increase with the further normalization during TH treatment and significant impovements in the mesenteric and renal blood flow on days 1–3 after TH treatment. We also suppose these improvements to be associated with the discontinuation (or substantial reduction) of inotropic / vasopressor support.

The comparative assessment with the results obtained in other studies could not be performed, since the resistive index was measured for predicting the development of MODS using an innovative approach (RF patent, registration number 2585143).

In general, the study group had severe and stable MODS during a 7-day follow-up period according to the SOFA score, whereas the control group showed some progression in the MODS course ($p<0.05$) during a 3–4 day follow-up. This indirectly confirmed our hypothesis.

The assessment of clinical effectiveness in neurosurgical patients after TH treatment without sedation reported that the Yunt-Hess and NIHSS scoring decreased (from 3. 8 [3.2; 4.1] up to 2. 1 [1.6; 2.9] and from 15. 8 [12.2; 21.6] up to 11. 3 [9.1; 15.4], respectively). The Lindegaard index decreased form critical value up to the acceptable one (from 4. 3 [3. 6; 4. 9] up to 1. 9 [1. 2, 2. 4]). Taking into account 100 % predicted mortality rate for all patients, mortality rate for neurosurgical patients was 26.6 % (11) vs. 33.3 % (3) in the control group. Mortality rate in cardiac patients was 57.1 % (8) vs. 70 % (7) in the control group. There were no signs of post-hypoxic encephalopathy observed among the survivors (100 % in the control group). Moreover, there were no critical values of CI (the development of secondary cardiogenic shock). Nevertheless, several non-fatal complications developed, namely arrhythmia — 6 (12.2 %); pneumonia — 4 (8.2 %); rebound hyperthermia — 7 (14.3 %). Similar complications were observed in other studies (5; 9). There were no cases of local skin damage and bleedings.

However, the present study has several limitations. First, a small number of patients were recruited to the study because of the randomization requirements. There were some difficulties to enroll patient into the control group, including ethical reasons. Unfortunately, it was impossible to assess the impact of basic MODS algorithm for

Table 3

Regional perfusion according to the resistive index, Me [25%, 75%]

	Baseline	During TH	Day 1	Day 3	Norms
Mesentric artery resistive index					
TH-	0.7 [0.67; 0.88]	0.56 [0.49; 0.59]	0.49 [0.48; 0.59]	0.49 [0.46; 0.59]	0.6
TH +	0.71 [0.69; 0.87]	0.58 [0.50; 0.61]	0.35 [0.29;0.39]	0.36 0.30; 0. 41]	0.6
Renal arterial resistive index					
TH-	0.8 [0.79;1.2]	0.64 [0.60;0.77]	0.54 [0.27; 0.59]	0.58 [0.48; 0.67]	0.6
TH +	0.8 [0.67;0.9]	0.67 [0.65; 0.78]	0.22 [0.19; 0.39]	0.39 [0.37;0.49]	0.6

Note: TH (-) — patients without TH; TH (+) — patients with TH

intensive care. The need to assess immunologic indicators and systemic inflammation to determine their role in the development of MODS.

Therefore, new insights presented in this article open an array of issues that should be addressed in the future studies. The adequate time period to induce TH treatment as well as its beneficial duration are still unclear. Optimal methods for objective control need further investigation (including the termination of TH). One of the issues is related to the choice of adequate treatment strategy when one of the following parameters — cerebral perfusion pressure, intracranial pressure or vasospasm — normalizes and others are not. The role of basal metabolism rate should be studied, since it may be a potential parameter suitable for monitoring of the effectiveness of TH treatment. The contribution of TH treatment combined with other methods to reduce intracranial pressure and blood flow velocity require additional studies (triple-H therapy, nimodipine, hormones, barbiturates, osmotic diuretics). The problem of hemostasis — anticoagulants or desagregants? Serial imaging and the need for neurological pause. The need for sedation and muscle relaxation, i. e. if there is no muscle manifestations, is it necessary to use sedation and muscle relaxation in these patients? All these issues require multicenter, randomized trials with full instrumental monitoring. Nevertheless, the results obtained in the present study allow us to make preliminary conclusions.

Conclusion

The initiation of non-invasive TH does not interfere with other management strategies. TH combined with other intensive care modalities appears to be an effective option for protecting organs against the deleterious effects of hypoxia. The initiation of TH, particularly in neurosurgical patients, requires advanced monitoring. TH is a high effective modality in intensive care of nontraumatic subarachnoid hemorrhage.

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ЗМІНИ ФУНКЦІОНАЛЬНОГО СТАНУ ТРОМБОЦИТІВ У ХВОРИХ НА ГОСТРИЙ ПАНКРЕАТИТ

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ИЗМЕНЕНИЯ ФУНКЦИОНАЛЬНОГО СОСТОЯНИЯ ТРОМБОЦИТОВ У БОЛЬНЫХ ОСТРЫМ ПАНКРЕАТИТОМ

Актуальность. Острый панкреатит — это воспаление поджелудочной железы/парапанкреатической клетчатки. Как и каждое воспаление, оно спровождается изменениями гемостаза. Тромбоциты в этом процессе играют одну из ведущих ролей, поскольку являются компонентом сосудисто-тромбоцитарного гемостаза и большинство реакций ферментного гемостаза также происходит на стенке тромбоцита.

Целью этой работы было исследовать динамику морфофункционального состояния тромбоцитов у больных острым панкреатитом.

Материал и методы. Обследовано 18 больных (8 женщин и 10 мужчин), госпитализированных во Львовскую областную клиническую больницу с диагнозом «острый панкреатит средней степени тяжести» с 2010 по 2015 гг. Причиной острого панкреатита у 10 пациентов были желчнокаменная болезнь и микролитиаз, у 4 больных — алкоголь, а у 4 пациентов был диагностирован идиопатический панкреатит. Лечение проводили согласно общепринятым протоколам. Использовался микроскопический метод исследования формы тромбоцитов, оценивались ее изменения при спонтанной активации клеток после их получения с сосудистого русла. В основе методики лежит метод Fromovik и Milton (1982).

Результаты. У больных острым панкреатитом уже на 3-и сутки болезни было отмечено уменьшение интактных тромбоцитов (71,4±1,1; $p<0,05$) и увеличение количества активированных форм, что указывает на активацию сосудисто-тромбоцитарного звена гемостаза уже в начале заболевания. Сумма активных форм тромбоцитов на третий день болезни составила 23,8 % (норма 7,9–17,7 %). Увеличение интактных форм тромбоцитов зафиксировано только на 10-е сутки болезни у больных острым панкреатитом средней степени тяжести. Сумма активных форм тромбоцитов в этот период болезни составила 15,6 %.

Выводы. Предоставленные данные об изменении форм тромбоцитов при их стимуляции указывают на возможность использовать эти показатели при патологических состояниях, которые сопровождаются нарушением гемостаза. Внутрисосудистая активация тромбоцитов обусловлена многими причинами: изменениями сосудистой стенки, повреждением тканей и др. Во многих