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Passive targeted temperature management in the intensive care of severe neonatal hypoxic-ischemic encefalopathy

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Key points

Therapeutic hypothermia or targeted temperature management has been shown to improve outcome after perinatal asphyxia in large clinical trials. Controlled cooling has become the standard of care for newborns with hypoxic-ischemic encephalopathy but preference of its method still remains controversial. The efficacy and safety of passive "non-heating" targeted temperature management as well as feasibility and reliability of non-invasive transfontanel Doppler evaluation of cerebral blood flow and perfusion pressure after undergoing severe hypoxia-ischemia in term infants were obtained during the study.

Objective

The study clarifies the neuroprotective possibilities of passive targeted temperature management to 33-35.5°C in severe neonatal hypoxic - ischemic encephalopathy.

Methods

Single-center, cohort, prospective study without pre-randomization was performed in 51 full term newborns with severe HIE which were treated in NICU of Dnepropetrovsk Regional Children's Hospital (Ukraine). The evaluation of systemic and cerebral hemodynamics and assessment of central nervous system disorders were obtained during passive targeted temperature management at 33-35.5°C for 72 hours period.

Results

Passive targeted temperature management was found as simple, safe, effective and affordable method of neuroprotection in term infants which significantly reduce cerebral reperfusion complicated the acute period after undergoing severe hypoxia-ischemia in term infants. Cerebral perfusion pressure obtained by non-invasive method based on the Doppler evaluation of blood flow velocities in the front cerebral artery can be used in the clinical assessment of the efficacy of neuroprotective therapy in neonates.

Keywords: newborns, targeted temperature management, hypothermia, hypoxic – ischemic encephalopathy, cerebral blood flow

Introduction

Severe hypoxic-ischemic brain injury is an acute and topical issue as to intensive neonatology in Ukraine reaching 13% of all full term newborns vs. 0.4% in Europe. Developing of this, in fact, anoxic brain injury as well as ischemic stroke, brain and spinal lesions at birth lead to a high percentage of deaths and/or major neurological deficit with severe disabilities in infants of 1st year of life.

Despite significant advances in monitoring technology and knowledge of fetal and neonatal pathology perinatal asphyxia or, more appropriately, hypoxic-ischemic encephalopathy (HIE) remains a serious condition leading to significant mortality and long-term morbidity [1, 2]. Proven effective protocol would significantly improve the results of treatment after perinatal hypoxia-ischemia does not exist. Despite the development of

numerous methods of intensive therapy the optimal maintenance of neuronal function and optimization of neurological outcome remain controversial [2, 3, 4].

According to the Neonatal Resuscitation Program of the American Academy of Pediatrics (2010) common practices include such method as induced therapeutic hypothermia to 33.5-34.5°C during 72 hours in post resuscitation period [5]. As to controlled hypothermia in recent years some researchers proposed new definitions namely [6]:

1. The term "targeted temperature management" to replace "therapeutic hypothermia".
2. The descriptors (e.g., "mild") to be replaced with explicit targeted temperature management profiles.
3. There are weak recommendations to use the targeted temperature management to 33°C–35.5°C (vs. less structured management) in the treatment of term newborns who sustained asphyxia and exhibit acidosis and/or encephalopathy.

However still there are some open questions about benefit of head cooling comparing to total body cooling, normal values and the role of cerebral perfusion pressure in newborns, the pattern of autoregulation of cerebral blood flow and it's possible passive depending on the blood pressure, state of the art as to volume resuscitation and the possibility of using of synthetic colloids in neonates with severe HIE, the degree of influence of different modes of positive pressure ventilation on intracranial pressure and cerebral blood flow as well as secondary pharmaceutical neuroprotection [2, 7, 8, 9, 10].

Objective

To clarify the possibility of passive targeted temperature management to 33-35.5°C [11, 12, 13, 14, 15] as a method of neuroprotection in the intensive care of severe hypoxic - ischemic encephalopathy in term newborns.

Methods

Single-center, cohort, prospective study without pre-randomization was performed in 51 full term newborns which were treated in NICU of Dnepropetrovsk Regional Children's Hospital (Ukraine). The evaluation of systemic and cerebral hemodynamics and assessment of central nervous system disorders were obtained during passive targeted temperature management at 33-35.5°C for 72 hours period. Inclusion criteria were: gestational age ≥37 weeks, birth weight ≥2500 g, Sarnat scale estimation at II-III stages (HB Sarnat, MS Sarnat, 1976 in modification of A. Hill, II Volpe, 1994) [16]. Exclusion criteria included congenital heart diseases and central nervous system abnormalities, gestational age <37 weeks, birth weight <2500 g, postnatal age >72 hours after birth. Birth weight in the study group was 3461 ± 496 g, gestational age 39.5 ± 1.4 weeks, 28 girls (54.9%) and 23 boys (45.1%). All newborns beginning from admission to NICU during 72 hours were passively cooled to the targeted body core temperature of 33-35.5°C under continuous monitoring of esophageal temperature probe. For all the babies there were performed assisted positive-pressure ventilation, routine control of acid-base balance, monitoring of SpO_2 and $etCO_2$, control of systemic hemodynamics (heart rate, blood pressure, cardiac output), the estimation of consciousness by modified GCS (Glasgow - St Petersburg Coma Scale, A. Jova et al., 2005) [17], control of tissue perfusion by serum lactate level, cerebral hemodynamic evaluation by non-invasive method based on conventional ultrasound Doppler transfontanel measurement of blood flow in the front cerebral artery (arteria celiaca anterior, ACA) with estimation of systolic (Vs), diastolic (Vd), mean velocity (Vm) and calculation of resistance index (RI), pulsating index (PI) and cerebral perfusion pressure (cerebral perfusion pressure, CPP) by the formula of Aaslid R. (1986) [18, 19, 20]. The investigations were conducted at admission, within 24 hours from the time of admission, on the third day after the restoration of normothermia, and at the 5^{th} and 7^{th} day of treatment in the department.

Data	Admission	24 hours	3rd day	5th day	7th day	p-value
Core temperature, °C	35.1±1.6	34.8±0.9	34.6±1.0	36.9±0.4	36.8±0.2	p<0.01
Mean BP, mm Hg	52.3±9.2	56.7±8.2	58.3±10.3	62.6±12.6	61.9±10.0	p<0.001
pH	7.35±0.1	7.40±0.07	7.43±0.08	7.46±0.08	7.43±0.05	p<0.05
pCO_2, mm Hg	39.1±7.4	40.1±10.3	40.3±8.1	48.5±4.9	43.6±9.7	p<0,05
SpO_2, %	96.3±3.3	96.5±2.4	96.5±2.3	95.4±2.3	95.8±2.7	p<0.01
Serum lactate, mmol/l	10.5±6.0	-	6.5±4.8	-	6.2±5.3	p<0.05
GCS	7.5±1,8	7.4±1.9	8.1±2.0	10.4±2.4	11.8±2.6	p<0.05
ACA V_s, cm/s	22.3±8.4	26.5±8.1	27.6±8.6	31.5±9.3	35.7±10.4	p<0.01
ACA V_d, cm/s	7.9±5.1	7.3±4.7	9.4±4.6	11.1±5.9	11.7±4.9	p<0.01
ACA V_m, cm/s	12.7±5,9	13.7±5.5	15.5±5.6	17.9±6.8	19.7±6.4	p=0.0505
CPP, mm Hg	9.0±6.5	10.1±6.0	12.0±6.1	14.7±7.4	16.7±7.0	p=0.0505

TABLE 1. CLINICAL EVALUATION OF TREATMENT GROUP.

The evaluation of central and cerebral hemodynamics, metabolic assessment and level of consciousness in term newborns with severe hypoxic-ischemic encephalopathy on the background of passive targeted temperature management to 33-35.5 ° C.

Results

In all newborns targeted temperature profile was provided passively as "non-heating", i.e. external heating elements of the open infant care system were switched off. By reducing the esophageal temperature below 33.0°C the radial heating elements and gel mattress were switched on with a targeted core body temperature of 34.0°C. With an increase in esophageal temperature >35.5°C additional cooling was provided by placing of frozen refrigerant packs around the head and an additional fan blow to rise convective heat transfer. Thus the target temperature management 33-35.5°C was started: in 27.5% (14 babies) in the first 6 hours of life, in 64.7% (33 children) - in the range of 6-24 hours after birth and in 7.8% (4 children) during 24-36 hours after birth. In first 6 hours after admission target temperature of the body was failed to reach in 17 children (33.3%) of whom in 10 children (19.6%) even by the end of the first day in NICU. The average deviation from the top of the specified temperature target zone in these children was 1.6±0.8°C (p<0.05). Throughout the study target temperature completely was failed to reach only in 1 baby (1.96%). However in 100% of children during the entire period of treatment the core temperature did not exceed 37°C. Score of HIE at admission was Sarnat II in 35 children (68.6%), Sarnat III - in 16 children (31.4%). Apgar score at the 5th minute after birth was 0-3 points in 6 children (11.8%), 4-6 points in 20 children (39.2%) and more than 7 points in 25 children (49.0%). 100% of children required an assisted positive-pressure ventilation during the whole period targeted temperature management. One child died on the 2nd day of treatment, two newborns more died after 7th days. Thus, the overall mortality rate among the study group was 5.9% (p<0.001), mortality during the passive targeted

temperature management at 33-35.5°C was 2.0% (p <0.001). The data obtained during the study has been presented in table 1.

Discussion

Analysis of data presented in the table may be summarized as follows:

1. Within 72 hours after admission to the department it was succeeded to achieve a controlled temperature, core body passively by in the hallway 33-35.5°C. Deviations from the mean value of 34°C did not exceed 1.5°C.
2. During the period of passive targeted temperature management to 33-35.5 ° C there was no significant impairment of the acid-base balance. On the background of standard volume replacement, inotropic and vasopressor therapy stable hemodynamics was observed in normotensive type. Quick reducing of post-ischemic metabolic disorders was obtained which was accompanied by a significant decreasing of serum lactate after 72 hours from admission to NICU.
3. In the study group while maintaining the target body core temperature 33-35.5°C a stable positive neurological dynamics were shown accompanied by a progressive decrease in the depth of coma. After the restoration of normothermia there was intermittent reperfusion cerebral changes, however, did not lead to a re-aggravation of neurological deficit.
4. A consistent correlation between changes in cerebral perfusion pressure and restoration of the level of consciousness has been found. It did not obtained a similar influence of mean arterial pressure on the CPP which may indicate a preservation of autoregulation of cerebral blood flow in newborn infants in the acute period after undergoing cerebral hypoxia-ischemia.

Conclusions

1. Passive cooling aimed to the targeted temperature management under esophageal core temperature control is simple, safe, effective and affordable method of neuroprotection in term infants.
2. The use of passive targeted temperature management on the background of tight control of hemodynamics significantly reduce cerebral reperfusion which complicate the acute period after undergoing severe hypoxia-ischemia in term infants.
3. Cerebral perfusion pressure obtained by non-invasive method based on the Doppler evaluation of blood flow velocities in the front cerebral artery and calculated by the Aaslid R. formula (1986) probably does not reflect the true value of the CPP. However its changes in time are clearly correlated with the level of consciousness as assessed by a modified coma scale “Glasgow - St. Petersburg” and can be used in the clinical assessment of the efficacy of neuroprotective therapy in neonates.

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