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Research Article

Ophthalmological Assessment of Newborns with Hypoxic-Ischemic Encephalopathy after Therapeutic Hypothermia

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Abstract

Aim of the study: The aim of the study was to evaluate the visual organ in children with severe hypoxic-ischaemic encephalopathy treated with controlled hypothermia. **Material and method:** Controlled hypothermia was performed in the Neonatal Intensive Care Unit in Zabrze using the CritiCool & Cure Wrap System. Children were qualified and controlled by neonatologists. All children were treated with whole-body hypothermia for 72 hours with a target temperature of 33 to 34°C in analgosedation with full biophysical monitoring. After recovery from controlled hypothermia, an ophthalmic examination was performed. The study included 74 newborns, 148 eyes, 32 girls and 42 boys. Children were born with an average weight of 3196.5 kg in the mean 39 weeks of pregnancy. **Results:** In all newborns there were transparent optical centers, congestive hemorrhage was found in 6 eyes, purulent secretion in conjunctival sac in one eye, in one eye a slight hemorrhage to the anterior chamber was observed. In the examination of the fundus of the eye, the normal optic disc was found in all eyes - pale pink, horizontally at the bottom, with smooth contours. The spots in the examined neonates were typical pale pink, without reflex. Only in one case the retinal blood vessels were widened, which resulted from the general condition of the child's circulatory system. In one eye single loss of pigment epithelium on the distant periphery of the retina was found. In 9 newborns in both eyes small, diffuse pre- and intraretinal hemorrhages were observed, whereas in one child hemorrhages were massive. **Conclusions:** The most frequent changes observed in the eyeball in the first days after controlled hypothermia were pre- and intraretinal hemorrhages. Ophthalmic examination of children after controlled hypothermia allows for early implementation of local and general treatment in case of changes in the vision organ.

Keywords: Newborn; Hypoxic-ischemic encephalopathy; Therapeutic hypothermia; Ophthalmological examination; Retinal hemorrhage

Introduction

The use of hypothermia in the treatment of the effects of sudden cardiac arrest and injuries of the central nervous system was in the circle of interest already in the years 1940-1950, but only the use of moderate hypothermia in the 1980s gave satisfactory results in the treatment of hypoxemic brain damage [1,2]. Clinical effects of hypothermia are influenced not only by the benefits of lower body temperature, but also to a great extent by the rate of hypothermia induction, its duration and the duration of normothermia restoration [1].

Hypoxic Ischemic Encephalopathy (HIE) resulting from perinatal hypoxia is the main cause of cerebral palsy and neurodevelopmental deficits in the group of reported newborns. The incidence of encephalopathy is about 2-6 per 1000 live-born newborns [3-5].

As a result of severe hypoxic injury, two phases of biochemical brain damage occur. In the initial phase, the neurons die immediately, and after reperfusion there is a period of latency with a short-term return of energy metabolism. This results in accumulation of cytokines, brain edema and oxidative mechanisms failure, a secondary phase leading to delayed death of neurons. Between the primary injury and the secondary phase, there is a latent phase, which lasts about 6 hours and is the so-called therapeutic window. The duration of the latent phase is inversely proportional to the severity of the ischaemic-isoxic injury [3,5]. Newborns born with perinatal hypoxia symptoms are treated in the Neonatal Intensive Care Units, but the commonly used drugs did not show beneficial neuroprotective effects [6]. Studies on biochemical and pathomorphological changes carried out on animal models undergoing experimental hypoxia confirmed the beneficial effect of hypothermia applied in the first hours after resuscitation on biochemical processes and distant neurological effects [3,7].

Ophthalmological examination of newborns in intensive care units is one of the additional examinations designed to exclude congenital changes in the eyesight, as well as disorders resulting from intrauterine infections, metabolic diseases or resuscitation carried out in the first minutes of a child's life.

Aim

The aim of our study was to evaluate the visual organ in children with severe hypoxic-ischemic encephalopathy treated with controlled hypothermia.

Material and Methods

Controlled hypothermia was performed in the Neonatal Intensive Care Unit in Zabrze using the CritiCool & Cure Wrap System. Children were qualified and controlled by neonatologists. Criteria for inclusion included: acute hypoxia incident, HIE symptoms, seizures, aEEG changes, long-term resuscitation, Apgar in 5 and 10 minutes <5, cord blood ph <7.0 and umbilical cord blood deficiency <-18BE, in particular up to 6 hours after an acute hypoxia incident. The exclusion criteria were lack of parental consent for treatment, head injuries or skull cracks causing CNS bleeding, anal obstruction, body weight under 1800 g, pregnancy age <36Hbd, large developmental defects, prophylactic high doses of anticonvulsants >20mg/kg phenobarbital [10]. In all children the whole body hypothermia was applied for 72 hours with the target temperature of 33 to 34°C in analgosedation with full biophysical monitoring, newborns were intubated, a catheter was placed in the umbilical cord vein and bladder, bloody RR measurement line and a thermometer in the anus [2,10].

The study included 74 newborns, 148 eyes, 32 girls and 42 boys. Children were born with an average weight of 3196.5 kg in the average 39 weeks of pregnancy. Among the evaluated newborns 38 (51.35%) were born by Caesarean section, the remaining 36 (48.65%) by forces of nature. Average pH of umbilical cord blood after birth was 6.99 (±0.22) in the studied group of children, while the deficiency of alkalis in umbilical cord blood BE -16.67(±7.13).

Newborns were evaluated on the Apgar scale 1, 3, 5 and 10 minutes after birth. In the study group, the mean Apgar at 1 minute of life was 1.53, at 3 minutes 2.64, at 5 minutes 3.79, and at 10 minutes 4.54. The mean Apgar at 1 minute of life was 1.53, at 3 minutes 2.64, at 5 minutes 3.79, and at 10 minutes 4.54.

All children were artificially intubated and ventilated in SIMV (Synchronized Intermittent-Mandatory Ventilation) mode, then cPAP (Continous Positive Airway Pressure), 3 children required support in HFO (High Frequency Oscillatory Ventilation) mode, also in 3 newborns HFPPV (High Frequency Percussive Ventilation) and in 2 IPPV (Intermittent Positive Pressure Ventilation). Changes in the central nervous system in the studied group of neonates are presented in Table 1.

CNS (Central Nervous System) disorders	Number	Percentage
Intraventricular haemorrhage (IVH Iº)	4	5.4
Malacia	1	1.35
Free flow in a transverse bay	1	1.35
Hypoxic ischemia changes	21	2.84
Transverse sinus thrombosis and esophagus thrombosis	3	4.05
Supraglottic haematoma	5	6.75
Hilly Vasculopathy	1	1.35
Brain oedema	2	2.7
Abnormal flow in the cerebellar arteries	1	1.35
Vascular plexus cyst	1	1.35
Ischemic stroke	1	1.35

Table 1: Changes in the central nervous system in the studied group of neonates.

An ophthalmic examination was performed in neonates in the first week after the controlled hypothermia. The examination was carried out with a manual fissure lamp and Fison's sight glass after dilatation of pupils obtained by administration to the conjunctival sac of 0.5% Tropicamide and 2.5% Phenylephrine hydrochloride solution. Before the examination, anaesthetic drops of Alcaine were injected into the conjunctival sac and retractors were placed as standard, and the eye recess was used during fundus viewing.

Results

In all newborns, there were transparent optical centers, congestive hemorrhage was found in 6 eyes, abscess secretion in conjunctival sac in one eye, in one eye a slight hemorrhage to the anterior chamber was observed, which was gradually resorbed during subsequent examinations of the child (Table 2).

Changes in the anterior segment of the eyeball	Number eyes	Percentage
Abnormal secretion in the conjunctival sac	1	0.67
Displacement spout	6	4.05
Hemorrhage to the anterior chamber	1	0.67

Table 2: Changes in anterior segment of the eye.

In the examination of the fundus of the eye a normal optic disc was found in all eyes - pale pink, horizontally at the bottom, with smooth contours. The spots in the examined neonates were typical pale pink, without reflex. Only in one case the retinal blood vessels were widened, which resulted from the general condition of the child's circulatory system. In one eye single loss of pigment epithelium on the distant periphery of the retina was found. In 9 newborns in both eyes small, diffuse pre- and intraretinal haemorrhages were observed, whereas in one child haemorrhages were massive. On the order of an ophthalmologist, these children received Etamsylate (Cyclonamine) and locally into the conjunctival sac Troxerutin (Posorutin). In subsequent examinations of the fundus of the eye a gradual resorption of hemorrhages was observed (Table 3).

Changes to the fundus of the eye	Number eyes /Percentage	Number baby/Percentage
Losses of RPE	1 / 0.67	1/ 1.35
Pre- and intraretinal haemorrhages	20/ 13.51	10/ 13.51
Vasodilation of the retina	2/ 1.35	1/ 1.35

Table 3: Changes in the fundus of the eye.

Overview

Many clinical trials have confirmed that the survival without severe neurological abnormalities was significantly more frequent in cooled newborns. Azzopardi et al. in a randomized Toby Trial study found that hypothermia reduces brain damage in ischemic-isoxic encephalopathy [8]. Neuroprotective effects of hypothermia result from a decrease in cerebral metabolism during hypothermia. Under these conditions, the consumption of ATP is slowed down despite the lack of oxygen and glucose supply, and the ionic pumps remain efficient for longer. Thus, hypothermia prevents neurons from being damaged by apoptosis, reduces the release of glutamate, inhibiting the pathological stimulation of neurons and the influx of calcium ions into cells. It significantly reduces the release of reactive oxygen species and slows down peroxidation processes [9]. Shah [11] analysed 13 studies published in 1998-2009 analyzing a total of 1440 children with perinatal hypoxia who were randomly assigned to a group with controlled hypothermia or treated with normothermal therapy. All newborns received standard treatment at the same time. The efficacy of treatment was assessed after 12 months of age. Among the general factors, 535 newborns were evaluated for severe visual impairment. RR (Relative Risc) was 0.59 (0.35-0.98) and NNT (Number needed to treat) was 20 (9-100). The author emphasized, however, that although controlled hypothermia is a safe and effective method of treatment of encephalopathy caused by perinatal hypoxia, colds of anoxidized organism can be carried out only in cases where the beneficial effects of this treatment outweigh the risk associated with hypothermia. Cold-injury syndrome, a potential complication of therapeutic hypothermia can result in sclerema, multisystem organ damage, especially intravascular coagulopathy, hypovolemia, glucose instability, reversible cardiovascular effects, elevated liver enzymes, late coagulopathy [12-18].

Few authors evaluating the effects of controlled hypothermia in children with perinatal hypoxia assess the ophthalmic state after recovery from hypothermia. In her work, Jacobs et al. [19] assessed the neurological condition 2 years after controlled hypothermia. Among many parameters evaluated by the authors there was also legal blindness, which was found in 1 case (1.3%) in the group treated with hypothermia compared to the lack of legal blindness in the control group. Shankaran, et al. [20] in turn evaluated children treated with hypothermia and treated typically at the age of 6-7 years after perinatal hypoxia. The authors found visuospatial dysfunction in 4% of children treated with hypothermia and in 3% of children without controlled hypothermia (P=0.80). The frequency of blindness in children in the study group of 1% and in the control group of 4% was not statistically significant.

In our study, we evaluated the ophthalmic condition of children in the first week after the end of controlled hypothermia. It was a standard ophthalmic consultation in children treated in neonatal intensive care units. In our group of examined children after controlled hypothermia, changes in 23 eyes (15.54% of eyes) were found, whereas preretinal hemorrhages were found in 20 eyes - in 10 children (13.51% of eyes), of which massive retinal hemorrhages significant for future vision disorders in both eyes of one child - 2 eyes (1.35% of eyes).

The literature also includes ophthalmological examinations of healthy children. Venekar, et al. [21] evaluated 1021 healthy full-term newborns within 72 hrs. of birth. Of this group of newborns, 48 babies had abnormal findings (4.7%). Retinal hemorrhages were the most common (52.1%) abnormality of which 24% were macular. Retinal hemorrhages were 2.4% of all babies screened. Callaway et al. [22] report the birth prevalence, risk factors, characteristic and location of fundus hemorrhages of the retina and optic nerve present in newborns at birth. The birth prevalence of fundus hemorrhages in this study was 20.3% (41/202 infants). 95% involved periphery, 83% involved the macula, and 71% involved multiple layers of the retina. Vaginal delivery was associated with a significantly increased risk of fundus hemorrhages. Similarly, in our group of examined children after controlled hemorrhage hypothermia, preretinal hemorrhages occurred in 80% of children born by natural forces and in 20% of children born by caesarean section. In the another study Ma, et al. [23] enrolled 481 infants at 45.1±6.1 days after birth. 198 infants had abnormal findings (41.2%). Retinal white spots and retinal white areas were the most common findings (42.9% of abnormalities and 17.7% of all infants screened). The second major finding was retinal hemorrhage (16.2% of abnormalities and 6.7% of all infants screened). In our study, white spots on the circumference of the bottom of the eye were found in 1 eye of one child, which constituted 0.67% of the examined eyes.

One of the largest multicentre studies was the analysis carried out by Tang, et al. [24]. Fundus examination were performed on newborns within the 42 days after birth. A total of 199851 newborns were included in this study. Authors detected 9.11% abnormal cases. The most frequent abnormality was severe retinal hemorrhages found in 6.41% cases.

Studies including ophthalmic evaluation of newborn babies born at a time without signs of perinatal hypoxia indicate the presence of retinal hemorrhages in a significant proportion of newborn babies. The majority of these studies are carried out one month after birth, which may to some extent underestimate the number of children with retinal hemorrhages due to their spontaneous absorption over time. Nevertheless, in our group of children with perinatal hypoxia undergoing controlled hypothermia therapy, we did not find a significantly higher number of hemorrhages at the fundus of the eye compared to the studies

carried out by many authors in the group of healthy reported newborns.

Universal eye screening of neonates is currently not standard of care even in developed countries. Early detection of abnormalities could offer prompt management and a reduction in visual morbidity.

Conclusions

The most frequent changes observed in the eyeball in the first days after controlled hypothermia were pre- and intraretinal hemorrhages. Ophthalmic examination of children born with features of perinatal hypoxia treated with controlled hypothermia allows for early implementation of topical and general treatment in case of the presence of hemorrhages at the bottom of the eye. Moreover, when evaluating the frequency of vision changes in children under controlled hypothermia, no significant number of ophthalmological complications was found in comparison with the results of studies on healthy neonates, which did not require intensive general treatment.

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