MEDDOCS Open Access Publisher

Annals of Ophthalmology and Visual Sciences

Open Access | Review Article

Ophthalmological Examination of Newborns with Hypoxic-Ischemic Encephalopathy Treated with Therapeutic Hypothermia

Bogumila Wojcik-Niklewska[1]*; Monika Sarnat-Kucharczyk[2]; Erita Filipek[1]; Jerzy Sobczyk[3]; Janina Kohut[3]

[1]Department of Pediatric Ophthalmology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland.

[2]Department of Ophthalmology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland.

[3]Department of Neonatological Intensive Care, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Zabrze, Poland.

***Corresponding Author: Bogumila Wojcik Niklewska**

Department of Pediatric Ophthalmology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland.

Tel: +48602319050;

Email: bogumila_wojcik_niklewska@op.pl

Received: Mar 28, 2021

Accepted: May 05, 2021

Published Online: May 07, 2021

Journal: Annals of Ophthalmology and Visual Sciences

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Hypothermia; Newborn; Ophthalmology; Hypoxic-ischemic encephalopathy; Retina.

Abstract

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

Methods: Controlled hypothermia was performed in the Neonatal Intensive Care Unit in Zabrze using the CritiCool & Cure Wrap System. Children were qualified and examined 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 through biophysical monitoring. After recovery from controlled hypothermia, an ophthalmic examination was performed. The study included 74 newborns.

Results: In all newborns transparent optical media were found. Subconjunctival hemorrhage was present in 6 eyes. Only in one case, the retinal blood vessels were dilated as a consequence of circulatory system disorders.

Conclusions: Ophthalmic examination of children after controlled hypothermia allows early implementation of local and general treatment in case of abnormality.

Abbreviations: HIE: Hypoxic-Ischemic Encephalopathy; aEEG: amplitude integrated electroencephalography: BD: Base Deficit; CNS: Central Nervous System; SIMV: Synchronized Intermittent-Mandatory Ventilation; cPAP: Continuous Positive Airway Pressure; HFO: High Frequency Oscillatory Ventilation; HFPPV: High Frequency Percussive Ventilation; IPPV: Intermittent Positive Pressure Ventilation; RR: Relative Risk; NNT: Number Needed to Treat.

Cite this article: Wojcik-Niklewska B, Sarnat-Kucharczyk M, Filipek E, Sobczyk J, Kohut J. Ophthalmological Examination of Newborns with Hypoxic-ischemic Encephalopathy Treated with Therapeutic Hypothermia. Ann Ophthalmol Vis Sci. 2021; 4(1): 1011.

Background

The use of hypothermia in the treatment of the effects of sudden cardiac arrest and injuries to the central nervous system became of interest already in the years 1940-1950, but it was only the use of moderate hypothermia in the 1980s that gave satisfactory results in the management of hypoxemic brain damage [1,2]. Clinical benefits of hypothermia not only depend on lowering of body temperature, but also on the rate of hypothermia induction, its duration and the rate of normothermia restoration [1].

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

Severe hypoxic injury is associated with two phases of biochemical brain damage. In the initial phase the neurons die immediately; after reperfusion there is a period of latency with a short-term return of energy metabolism. This leads to the secondary phase with accumulation of cytokines, brain edema and failure of oxidative mechanisms ultimately resulting in delayed neuronal death. Between the primary injury and the secondary phase there is a latent phase, which lasts about 6 hours and is referred to as the therapeutic window. The duration of the latent phase is inversely proportional to the severity of the ischemic-hypoxic injury [3,5]. Newborns 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 in animals undergoing experimental hypoxia confirmed the beneficial effect of early post-resuscitation hypothermia on biochemical processes and late neurological effects [3,7].

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

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

Methods

Retrospective study with controlled hypothermia was performed in the Neonatal Intensive Care Unit in Zabrze using the CritiCool & Cure Wrap System. Children were qualified and examined by neonatologists. The inclusion criteria were acute hypoxia incident, HIE symptoms, seizures, changes in amplitude integrated Electroencephalography (aEEG), long resuscitation, *5 and 10 minute Apgar scores* <5, cord blood pH <7.0 and *Base Deficit* (BD) *of umbilical-cord* arterial *blood*<18, and, in particular, time within 6 hours of an acute hypoxia incident. The exclusion criteria were lack of parental consent for treatment, head injuries or skull cracks causing Central Nervous System (CNS) bleeding, anal obstruction, body weight under 1800 g, pregnancy week <36, serious developmental defects, high doses of anticonvulsant prophylaxis >20mg/kg of phenobarbital [10]. All children underwent 72-hour whole-body hypothermia with the target temperature of 33 to 34°C in analgosedation with full biophysical monitoring. The newborns were intubated; a catheter was placed in the umbilical cord vein and bladder, and a thermometer in the anus. *Intra-arterial* catheters were inserted for *invasive blood pressure* monitoring [2,10]. The study comprised 74 newborns, 148 eyes, 32 girls and 42 boys. Children were born with an average weight of 3196.5 kg and, on average, in the 39 week of pregnancy. Thirty-eight (51.35%) children were delivered by Caesarean section, the remaining 36 (48.65%) were vaginal deliveries. The average pH of umbilical cord blood after birth was 6.69 (±0.22); base deficit of umbilical-cord arterial blood was 16.67(±4.13).

The newborns were evaluated on the Apgar scale 1, 3, 5 and 10 minutes after birth. The mean Apgar score 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 intubated and ventilated in Synchronized Intermittent-Mandatory Ventilation (SIMV) mode, then Continuous Positive Airway Pressure (cPAP). Three children required support with High Frequency Oscillatory Ventilation (HFO) mode. High Frequency Percussive Ventilation (HFPPV) was used in three and Intermittent Positive Pressure Ventilation (IPPV) in two children.

Changes in the central nervous system are presented in Table 1.

An ophthalmic examination was performed in all neonates in the first week after the controlled hypothermia. The examination was carried out with a manual slit lamp and Fison binocular indirect ophthalmoscope after pupil dilatation by instillation of 0.5% tropicamide and 2.5% phenylephrine hydrochloride solution into the conjunctival sac. Before the examination, a topical anaesthetic, *proxymetacaine* hydrochloride *0.5%*, was instilled into the conjunctival sac, eyelid speculum was placed and globe indentation was applied during fundus examination.

Results

All newborns had transparent optical media. Subconjunctival hemorrhages were found in 6 eyes, purulent discharge in conjunctival sac in one eye. Mild anterior chamber hemorrhage was noted in one eye, which then gradually resorbed. Anterior segment changes are presented in Table 2.

In all examined eyes, normal pink pale optic disc with smooth margin and pale pink macula without reflex were found. Only in one case, the retinal blood vessels were dilated as a consequence of circulatory system disorders. Slight retinal pigment epithelium defects in the peripheral retina were noted in one eye. Nine newborns had diffuse bilateral pre- and intraretinal hemorrhage; one child had massive hemorrhage.

Intravenous cyclonamine (Etamsylate®) and troxerutin (Posorutin®) were instilled into the conjunctival sac as instituted by the ophthalmologist. Subsequent fundus examination revealed gradual hemorrhage resorption. Table 3 presents fundus changes.

Table 1: Central nervous system changes.

Central Nervous System Changes	Number	Percentage
Intraventricular hemorrhage (IVH) I°	4	5.4
Malacia	1	1.35
Slow flow in transverse venous sinus	1	1.35
Hypoxic-ischemic changes	21	2.84
Transverse venous sinus thrombosis and sigmoid venous sinus thrombosis	3	4.05
Supradural hematoma	5	6.75
Thalamic vasculopathy	1	1.35
Brain edema	2	2.7
Abnormal flow in the cerebellar arteries	1	1.35
Choroid plexus cyst	1	1.35
Ischemic stroke	1	1.35

Table 2: Anterior segment changes.

Anterior Segment Changes	Number Of Eyes	Percentage
Purulent discharge in the conjunctival sac	1	0.67
Subconjunctival hemorrhage	6	4.05
Hemorrhage in the anterior chamber	1	0.67

Table 3: Fundus changes.

Fundus Changes	Number Of Eyes	Percentage
RPE loss	1	1.35
Pre- and intraretinal hemorrhage	20	13.51
Dilated retinal vessels	2	1.35

Discussion

Many clinical trials have confirmed that survival without severe neurological abnormalities was significantly more frequent in newborns treated with controlled hypothermia. A randomized Toby Trial by Azzopardi et al. showed that hypothermia reduced brain damage in ischemic-hypoxic encephalopathy [8]. Neuroprotective effects of hypothermia result from a decrease in cerebral metabolism. 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. Hypothermia prevents neurons from being damaged by apoptosis, reduces the release of glutamate thus 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] reviewed the reports from 13 clinical trials published between 1998-2009 comprising a total of 1440 children with perinatal hypoxia treated with controlled hypothermia or normothermic therapy. All newborns also received standard treatment. The efficacy of treatment was assessed at the age of 12 months. Among the general parametries, 535 newborns were evaluated for severe visual deficit. Relative Risk (RR) was 0.59 (0.35-0.98) and Number Needed to Treat (NNT) was 20 (9-100). The author emphasized that although controlled hypothermia was a safe and effective method of treatment for perinatal hypoxia-induced encephalopathy, temperature reduction of hypoxic organism can be carried out only when the expected benefits 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, glucose instability, hypovolemia, reversible cardiovascular effects and late coagulopathy [12-18].

Only few authors evaluating the effects of controlled hypothermia in children with perinatal hypoxia have assessed the ophthalmic status after recovery from hypothermia. Jacobs et al. [19] assessed the neurological condition at 2 years of age, ie., 24 months after controlled hypothermia. Among numerous parameters evaluated by the authors was legal blindness, which was found in 1 patient (1.3%) in the group treated with hypothermia compared to absence of legal blindness in the control group. Shankaran et al. [20] evaluated children aged 6-7 years who had suffered neonatal hypoxic–ischemic encephalopathy and had received hypothermia or usual care. Visuospatial dysfunction was found in 4% of the children treated with hypothermia and 3% of those receiving usual care (P=0.80). The rates of blindness were 1% and 4% in the hypothermia and usual care group, respectively. The difference was not statistically significant.

In our retrospective study we evaluated the ophthalmic condition of 74 children in the first week following controlled hypothermia. It was a standard ophthalmic consultation in children treated in neonatal intensive care units; changes were found in 23 eyes (15.54%). Preretinal hemorrhage was observed in 20 eyes of 10 children (13.51%) including massive bilateral retinal hemorrhage with vision threatening potential in one child - 2 eyes (1.35%).

The literature also includes reports on ophthalmic examinations of healthy children. Vinekar et al. [21] evaluated 1021 healthy full-term newborns within 72 hours of birth. Forty-eight babies had abnormal findings (4.7%). Retinal hemorrhages were the most common abnormality (52.1%) seen in 2.4% of all babies screened. Callaway et al. [22] report the birth prevalence, risk factors, characteristics and location of fundus hemorrhages of the retina and optic nerve present in newborns at birth. The prevalence of fundus hemorrhages was 20.3% (41/202 infants) of which 95% involved the 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. Our results are comparable – preretinal hemorrhages were diagnosed in 80% and 20% of the vaginally- and cesarean-delivered babies, respectively. (Czy powyższe zdanie jest poprawne gramatycznie?) 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 in the fundus periphery were found in 1 eye, which constituted 0.67% of the examined eyes.

One of the largest multicenter studies was the analysis carried out by Tang et al. [24]. Fundus examination was performed in newborns within 42 days after birth. A total of 199 851 newborns were included in this study. The authors detected 18 198 (9.11%) abnormal cases. The most frequent abnormality was severe retinal hemorrhage found in 6.41% of the study population.

Studies including ophthalmic evaluation of full-term babies born without signs of perinatal hypoxia indicate the presence of retinal hemorrhages in a significant proportion of newborns. The majority of these studies are carried out at one month after birth, which may, to some extent, result in underestimating the number of children with retinal hemorrhages due to their spontaneous absorption over time. Nevertheless, our newborns with perinatal hypoxia treated with controlled hypothermia did not exhibit a significantly higher number of fundus hemorrhages compared to that revealed by other authors.

At present, newborn eye screening is not a standard of care even in developed countries though it should be noted that early detection of abnormalities could contribute to prompt management and reduction in visual morbidity.

Conclusions

The most frequent changes observed in the eye in the first days after controlled hypothermia were pre- and intraretinal hemorrhages. Ophthalmic examination of newborns with perinatal hypoxia treated with controlled hypothermia allows early implementation of topical and general treatment in case retinal hemorrhage is diagnosed. Furthermore, eye evaluation in children undergoing controlled hypothermia did not reveal significant differences compared to the studies on healthy neonates who did not require intensive general treatment.

Declaration

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki.

The study protocol complied with national guidelines:

Gulczynska E, Gadzinowski J. [Therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy]. Ginekol Pol. 2012 Mar; 83: 214-8. Review. Polish. https://www.ncbi.nlm.nih.gov/pubmed/22568198

and did not require bioethics committee approval.

Informed written consent was obtained from all individual participants' parents included in the study.

Consent for Publication

Written consent for publication was obtained from all individual participants' parents included in the study.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Authors' Contributions

BWN drafted the manuscript and performed the literature review. JS, JK participated in information gathering and editing. Additionally, EF revised the manuscript and provided direction of discussion. MSK assisted in revising manuscript and also offered critical advice regarding discussion. All authors read and approved the final manuscript.

Acknowledgement

The authors are indebted to technicians and research assistants.

References

1. Rybicki Z, Tomaszewski D. [Hypothermy in the treatment of life-threatening conditions. Current state of knowledge]. Lekarz Wojskowy. 2009; 4: 295-300.
2. Gupta S, Sinha S. Brain cooling and hypoxic encephalopathy-myth or reality?. Archives of Perinatal Medicine. 2005; 11: 27-29.
3. Gulczynska E, Gadzinowski J. Therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy. Ginekol. Pol. 2012; 83: 214-218.
4. Kornacka M, Bokiniec R, Bargiel A. Risc factors for preterm encephalopathy. Ginekol.Pol. 2009; 80: 620-623.
5. Allen KA, Brandon DH. Hypoxic Ischemic Encephalopathy: Pathophysiology and Experimental Treatments. Newborn Infant Nurs Rev. 2011; 11: 125-133.
6. Chaudhari T, McGuire W. Allopurinol for preventing mortality and morbidity in mewborn infants with suspected hypoxic-ischemic encephalopathy. Cochrane Database Syst Rev. 2008; CD 006817.
7. Haaland K, Loberg E, Steen T, Thoresen M. Posthypoxic hypothermia in newborn piglets. Pediatr Res. 1997; 41: 505-512.
8. Azzopardi D, Strohm B, Edwards S. TOBY Study Group. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med. 2009; 361: 1349-1358.
9. Pagowska-Klimek I, Krajewski W. Zastosowanie hipotermii kontrolowanej w intensywnej terapii. Anestezjologia intensywna Terapia. 2010; 42: 167-173.
10. Kołomyjec A, Kornacka MK. Hipotermia w leczeniu encefalopatii niedokrwienno-niedotlenieniwej u noworodka. Pediatria Polska. 2001; 6: 455-460.
11. Shah PS. Hypothermia: A systematic review and meta-analysis of clinical trials. Seminars in Fetal and Neonatal Medicine. 2010; 15: 238-246.
12. Blackmon LR, Stark AR. Hypothermia: A Neuroprotective Therapy for Neonatal Hypoxic-Ischemic Encephalopathy. Pediatrics. 2006; 117-942.
13. Azzopardi D, Robertson NJ, Cowan FM, Rutherford MA, Rampling M, Edwards AD. Pilot study of treatment with whole body hypothermia for neonatal encephalopathy. Pediatrics. 2000; 106: 684-694.
14. Battin MR, Penrice J, Gunn TR, Gunn AJ. Treatment of term infants with head cooling and mild systemic hypothermia (35,0°C and 34,5°C) after perinatal asphyxia. Pediatrics. 2003; 111: 244-251.
15. Eicher DJ, Wagner CL, Katikaneni LP. Moderate hypothermia in neonatal encephalopathy: safety outcomes. Pediatr. Neurol. 2005; 32: 18-24.
16. Gluckman PD, Wyatt JS, Azzopardi D. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet 2005; 365: 663-670.
17. Shankaran S, Laptook AR, Ehrenkranz RA. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med. 2005; 353: 1574-1584.
18. Culic S. Cold injury syndrome and neurodevelopmental changes in survivors. Arch Med. Res. 2005; 35: 532-538.
19. Jacobs SE, Morley CJ, Inder TE, Stewart MJ, Smith KR. Whole-body hypothermia fot Term and Near-Term Newborns With hypoxic-Ischemic Encephalopathy. A Randomized Controlled Trial. Arch Pediatr Adolesc med. 2011; 165: 692-700.

20. Shankaran S, Pappas A, McDonald SA, Vohr BR, Hintz SR. Childhood Outcomes after Hypothermia for Neonatal Encephalopathy. N Engl J Med. 2012; 366: 2085-2092.

21. Vinekar A, Govindaraj I, Jayadev C, Kumar AK, Sharma P. Universal ocular screening of 1021 term infants using wide-field digital imaging in a single public hospital in India – A pilot study. Acta Ophthalmologica. 2015; 93: e372-e376.

22. Callaway NF, Ludwig MA, Blimenkranz MS, Jones JM, Fredrick DR. Retinal and Optic Nerve Hemorrhages in the Newborn Infants: One-Year Results of the Newborn Eye Screen Test Study. Ophthalmology. 2016;123: 1043-1052.

23. Ma Y, Deng G, Ma j, Liu J, Li S. Universal ocular screening of 481 infants using wide-field digital imaging system. Ophthalmology. 2018; 18: 283.

24. Tang H, Li N, Li Z, Zhang M. British Journal of Ophthalmology. 2018; 102: 313481.