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Selective head cooling or whole body cooling? That is the question

Vlad Dima[1], Roxana-Elena Bohiltea[2,3], Raluca Mariana Stanescu[4], Adrian Toma[5], Valentin-Nicolae Varlas[2,3], Ana-Maria Davitoiu[3,6]

[1] Department of Neonatology, Filantropia Clinical Hospital, Bucharest, Romania
[2] Department of Obstetrics and Gynecology, Filantropia Clinical Hospital, Bucharest, Romania
[3] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[4] National Institute for Mother and Child Health "Alessandrescu-Rusescu", Bucharest, Romania
[5] Medlife Memorial Hospital, Bucharest, Romania
[6] "Victor Gomoiu" Clinical Hospital, Bucharest, Romania

ABSTRACT

Background. Studies to date support the beneficial effect that therapeutic hypothermia (TH) has on neonates with hypoxic-ischemic encephalopathy. TH can be delivered in two ways: selective head cooling (SHC) or therapeutic whole-body cooling (WBC). The purpose of this review is to examine the literature to expose the advantages and disadvantages of the two methods of performing TH in neonates diagnosed with moderate or severe HIE and to investigate whether one method is superior to the other.

Methods. We started from the data from the Cochrane review published in 2013 [1] and we want to bring new information from recent clinical studies comparing the two TH methods (SHC vs WBC). Clinical studies were searched and analyzed by a single individual (through dedicated search engines such as Google Scholar, PubMed, and Scopus). We have included clinical studies from the last 7 years comparing the two ways of performing TH (SHC vs. WBC). We selected only the articles that compared the two methods and excluded the articles describing only one method.

Results. After excluding the clinical trials that did not meet the eligibility criteria, 5 clinical trials remained (n = 256 neonates). Analysis of these studies supports the idea that both modalities of therapeutic hypothermia cool central nervous system (CNS) structures and have a similar neurodevelopmental prognosis among surviving neonates. Also, there are no significant differences in terms of short-term neurological prognosis, as well as the adverse effects that may occur in neonates with moderate or severe HIE (hypoxic-ischemic encephalopathy) treated with SHC or WBC; although some studies note the presence of more severe, statistically significant lesions among patients treated with SHC compared to those treated with WBC.

Conclusions. Prospective, randomized studies on a much larger scale are needed to track the adverse effects that the two HT methods may have on patients, as well as long-term neurological and cognitive prognosis. Until now, there is no clear evidence that one of these two methods is definitely safer or more reliable than the other.

Keywords: hypoxic-ischemic encephalopathy, therapeutic hypothermia, selective head cooling, whole body cooling, treatment, adverse effects

INTRODUCTION

For more than a decade HT is used as the first-line treatment for HIE. The neuroprotective benefits of this therapy have been demonstrated in multiple studies. A decrease in the risk of adverse reactions occurring following the institution of TH was observed, from 45% in the initial studies to 29% in the recent studies. This can be attributed to the reduction

Corresponding author:
Valentin Nicolae Varlas
E-mail: valentin.varlas@umfcd.ro

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in mortality from 25% in the initial studies to 10% in the most recent studies [1,9,10]. The mechanism underlying these decreases is still unknown, although it is assumed to be due to the earlier initiation of TH, the increasingly extensive experience that specialized medical personnel has acquired, the inclusion in the protocol of HT treatment of more and more newborns with mild HIE, as well as the addition of adjuvant treatments (such as erythropoietin).

HIE is an important consequence of severe perinatal asphyxia. HIE has an incidence of 1-2 per 1,000 live births in the Western world and is much more common in developing countries. Although metabolic syndromes can have clinical manifestations similar to perinatal asphyxia, and genetic and placental anomalies can contribute to the clinical picture, it has been demonstrated that there are specific acute changes in the brain of the newborn at term or near term who presented perinatal asphyxia [11,12].

The chance of irreversible damage or even death is high in newborns with severe perinatal asphyxia (up to 65% of patients enrolled in studies investigating the effectiveness of neuroprotective strategies in the treatment of HIE). Therapeutic hypothermia has a neuroprotective effect, as demonstrated in several studies, and is the standard therapy for near-term or full-term neonates with moderate or severe HIE if HT is initiated within the first 6 hours of life. It is also worth mentioning that, currently, attempts are being made to demonstrate the protective role of other substances that could provide increased neuroprotection in newborns treated by TH [10,13,14].

Despite the improved prognosis of many patients by treating them with TH, many questions remain that need to be answered in future studies aimed at improving the management of the neonate with HIE as a result of perinatal asphyxia. Among these questions, we find: Is TH beneficial in mild HIE? Is the current therapeutic window sufficient to ensure the best prognosis? Should late preterm infants with HIE be treated with TH? Is the thermal threshold of 33.5 °C optimal? Does WBC have too many adverse effects and would SHC be preferable? What other alternative therapies could be associated with HT to improve the patient's prognosis?

PATHOPHYSIOLOGY OF CEREBRAL HYPOXIC-ISCHEMIC LESIONS PRODUCED BY HIE

Perinatal asphyxia occurs in conditions of deficient gas exchange, caused, most frequently, by affecting the supply of oxygen from the placental level, and if this persists, hypoxemia and hypercapnia appear. In case of total interruption of the supply of oxygen at the placental level, within a few minutes, the cellular metabolism of the fetus becomes anaerobic, which leads to the production of lactic acid, contributing to the appearance of metabolic acidosis. The value of these compounds can be assessed by collecting blood from the umbilical cord. At the same time, metabolic acidosis contributes to the occurrence of bradycardia, which further worsens the systemic blood flow, producing brain ischemia, hypoxemia and hypercapnia specific to HIE [1,9,15].

A reduction in oxygen intake soon causes a drop in cellular phosphate levels, producing primary energy insufficiency. At the same time, the accumulation of lactic acid, as a result of the metabolism of glucose by anaerobic means, leads to the dysfunction of ion pumps at the membrane level. This contributes to the appearance of cellular edema. Calcium influx releases glutamate and ultimately leads to an excitotoxic cycle that results in the production of free radicals and nitric oxide, as well as lipid peroxidation of cell membranes, these processes contributing to cell necrosis. If cerebral blood flow is restored by means of resuscitation maneuvers, partial restoration of cellular metabolism may occur during the reperfusion period. A latent phase follows with varying duration depending on the severity of the insult. This can last from 6 to 48 hours, from the time of the initial insult. The latent phase can progress to a secondary energy failure, which is characterized by the presence of inflammation, oxidative damage and free radicals, as well as neuronal death by apoptosis. The severity of the injury determines the extent of brain damage. Current neuroprotective therapies are designed to intervene in the latent phase, before the onset of secondary energy failure [16,17].

THERAPEUTIC HYPOTHERMIA FOR LATE PRETERM INFANTS

Experimental studies have concluded that TH has a beneficial effect on the survival rate of term or near-term neonates with moderate or severe HIE. This cannot be extrapolated to late preterm infants without studies to prove this fact. Moreover, premature babies have an increased risk of intracranial hemorrhage if they are placed in a low-temperature environment. Also, due to the degree of immaturity of the nervous system, the evaluation of the degree of neurological damage is very subjective in premature patients with HIE. We still do not know how HIE manifests in newborns between 33-35 weeks of gestational age (GW), and we also do not know if HT has any benefit in this age category [10,18].

Preclinical studies on premature lambs have shown that HT has a protective effect on central nervous system (CNS) structures, as well as a reduction in apoptosis. It was also concluded that the fastest possible initiation of HT is essential for the best possible prognosis among lambs [18].

The encephalopathy that occurs secondary to a hypoxic-ischemic event in premature newborns is based on complex physiopathological mechanisms, given the fact that, in addition to perinatal asphyxia, premature newborns can also present deficiencies in the normal evolution of the CNS maturation process. We do not have concrete data on the actual incidence of HIE in late preterm newborns, as clear diagnostic criteria for this group have not yet been established. Due to the changes produced during the maturation of the neurological structures of preterm infants, we do not know if the criteria used for the selection of term newborns with HIE requiring the initiation of TH can be extrapolated too late preterm infants. We also do not know whether the imaging appearance of neurological lesions is similar to that of term neonates. At the same time, the neurological examination of premature newborns is more difficult because they have better developed archaic reflexes, as well as differences in the maturation of tone and posture. From all these aspects, it follows that the Sarnat test cannot be used with the same accuracy for the diagnosis of HIE among late preterm newborns as it is used among full-term or near-term newborns [19,20,21].

At the same time, animal experiments have shown that an immature brain is more resistant to hypoxia or ischemia, compared to the brain of a full-term newborn. Most reasons to explain this difference are a low rate of cerebral metabolism, lower sensitivity to neurotransmitters with neurotoxic potential, as well as greater plasticity of the immature CNS. However, in the term neonate as well as in the preterm neonate, HIE is a major cause of acute mortality and, in survivors, an important cause of morbidity [10,18,19].

MECHANISM OF ACTION OF THERAPEUTIC HYPOTHERMIA

HT aims to decrease the temperature at the level of the deep cerebral structures, which are vulnerable in the context of a hypoxic or ischemic event, to 32°C - 34°C. There are two methods by which HT can be performed in newborns with HIE:

- whole body cooling (WBC);
- selective cooling of the head with mild systemic hypothermia (SHC).

The reason why selective head cooling was chosen is that 70% of the total body heat is produced by the newborn's brain and that systemic hypothermia can be physiologically harmful to the sick newborn. Therefore, the adverse effects of systemic cooling can be minimized by selectively cooling the brain more than the body [1,22].

However, following the studies, it was observed that only by cooling the whole body to 34°C a significant reduction of temperatures in the deep structures of the brain could be achieved. It was also from this study that in order to reduce the temperature in the deep structures of the brain, the central temperature must be at least 35°C [2,3].

WBC is based on the fact that the core temperature of the body is similar to the temperature present in the deep structures of the brain [1,11].

Criteria for initiating therapeutic hypothermia [1,24]

The possibility that acute intrapartum or peripartum hypoxia or ischemia may have contributed to HIE is based on the following factors:

a. Apgar score of 5 or less at 10 minutes;

b. The need for continuous resuscitation with positive pressure ventilation +/- external cardiac massage, every 10 minutes

c. Umbilical artery pH <7 (sample taken in the first minutes of life) or a base deficit >12mmol/L 60 minutes after birth.

d. Evidence of encephalopathy according to Sarnat staging [24]:

- Stage 1 (mild): hypervigilance, hyperreflexia, mydriasis, tachycardia, absence of convulsions;
- Stage 2 (moderate): lethargy, hyperreflexia, miosis, bradycardia, convulsions, hypotonia with weak sucking reflex and weak Moro;
- Stage 3 (severe): stupor, severe hypotonia (flabby tone), mydriasis that reacts poorly to light, diminished tendon reflexes, hypothermia and the absence of the Moro reflex.

e. There are no major congenital anomalies recognized at birth.

f. Neuroimaging evidence of HIE-specific acute brain lesions seen on brain magnetic resonance imaging (MRI) or magnetic resonance spectroscopy.

g. Presence of multiple organ failure (MOSF) consistent with HIE.

THE NEUROPROTECTIVE ROLE OF THERAPEUTIC HYPOTHERMIA

An important factor contributing to the morbidity associated with HIE is the development of spastic tetraparesis. The global prevalence of spastic tetraparesis is 2-3 cases per 1000 births. Intrapartum hypoxia and acidosis contribute to approximately 10-20% of cases of spastic tetraparesis. TH initiation is required to prevent the installation of HIE-associated mobilities.

In the specialized literature, the existence of several mechanisms that could contribute to the neuroprotective role of TH has been demonstrated:

- hypothermia in the deep structures of the brain could stop the process of neuronal apoptosis that occurs in the latent phase of HIE; demonstrated in animal studies.

- hypothermia may protect brain cells by:
  - reduction of cerebral metabolism;
  - decrease in the release of substances with an exciting role (glutamate, dopamine);
  - decreased production of toxic compounds such as nitric oxide and free radicals.

In the first four pilot studies of therapeutic hypothermia in newborns, no important side effects were observed. Adverse effects such as bradycardia, hypertension, and increased oxygen demand were temporary and reversible once the newborn was warmed.

Studies show that therapeutic hypothermia has proven its neuroprotective role among newborns with perinatal asphyxia who developed moderate and severe forms of HIE. At the same time, the highest degree of neuroprotection is present among newborns with moderate HIE, compared to severe HIE [1,14,23,25].

The 2013 Cochrane review included 11 randomized controlled trials of WBC and SHC. This review included 1505 term or near-term neonates with moderate or severe HIE and evidence of intrapartum asphyxia. Therapeutic hypothermia resulted in a statistically significant reduction in mortality or major deficit survival up to 18 months of age (RR = 0.75 (95% CI 0.68-0.83)). A significant reduction was also observed of mortality (RR = 0.75 (95% CI 0.64 to 0.88)) and neurological retardation in survivors (RR = 0.77 (95% CI 0.63 to 0.94)). Adverse effects of therapeutic hypothermia were an increased frequency of episodes of sinus bradycardia and a significant increase in thrombocytopenia [1].

SELECTIVE THERAPEUTIC HYPOTHERMIA OF THE HEAD OR THERAPEUTIC HYPOTHERMIA OF THE WHOLE BODY?

A) In a prospective study on a group of 29 patients, published by Atyci et al. in 2015 [31], TH was initiated in two ways; SHC (n = 17) or WBC (n = 12), in neonates with a gestational age greater than 35 weeks. No difference was found, in terms of side effects, between the group of patients in which SHC was initiated and the WBC group. Also, in this study, no significant difference was found between the WBC group and the SHC group in terms of need for mechanical ventilation during the cooling phase. At the same time, there was no significant difference between the two groups (SHC vs WBC) in terms of the variables necessary to ensure good pulmonary ventilation, and no significant differences, between the SHC and WBC group, which could delay extubation of the patients after the interval of 72 hours.

B) Celik Y. et al. [32] published in 2016 a prospective study with a small number of patients (n=29), and they found no significant difference in adverse events between the two SHC (n = 17) and WBC (n = 12) groups. One neonate in each group died during the hospital stay, while six neonates in the SHC group (35%) and three neonates in the WBC group (25%) died after hospital discharge. There were no statistically significant differences in the frequency of episodes of hypotension, bradycardia, thrombocytopenia, abnormal coagulation times, abnormal renal function, fluid and electrolyte imbalances, elevated liver enzymes, culture-positive sepsis, persistent pulmonary hypertension, lung air leak syndrome (e.g. pneumothorax), the need to extubate the patient during the cooling phase or the worsening of respiratory function that requires increased ventilation parameters.

TABLE 1. Comparison of the selective head cooling group and the whole body cooling group in terms of adverse effects

Findings	Selective head cooling (n=17)	Whole body cooling (n=12)
	%	%
Hypotension	70	58
Bradycardia		
Platalet count <100000 µL	59	25
Abnormal coagulation tests	41	33
Renal dysfunction	29	33
Hyponatremia	53	42
Hypokalemia	29	25
Increased liver enzymes	65	50
Culture positive sepsis		
Edema in the scalp		
Hypocalcemia	59	74
Persistent pulmonay hypertension		
Lung air leak		
Requirement for invasive mechanical ventilation during the period of cooling	94	92

In addition, both TH methods showed similar results in terms of 12-month mortality, severe disability, and disability-free survival. Further studies in a larger cohort of patients with longer follow-up periods are needed to further compare the efficacy of SHC and WBC. This study is the first that compares the medium-term outcome of SHC and WBC.

C) Consistent with previous studies, a study from Gulczynska EM. et al. 2019 [33] concluded that neither of the two TH methods (SHC vs WBC) proved superior in this prospective study either. Although this study included the largest number of neonates investigated to date (n = 78 neonates), no additional clinical benefit was observed for the WBC technique. Despite the lack of clinical advantages, it must be emphasized that the WBC method is much simpler to use according to the protocol (due to the servo-control). Both methods of therapeutic hypothermia are equally effective. No significant differences in short-term outcomes and risk of adverse effects were found between SHC and WBC in neo-

TABLE 2. Outcomes of SHC and WBC

Outcomes during spitalization	SHC (n=17) n(%). median (IQR) or mean ± SD	WBC (n=12) n(%). median (IQR) or mean ± SD
Death	1/17 (6)	1/12 (8)
Hospitalization (days)	34 (14-48)	18 (11-43)
Discharged with tracheostomy	4/16 (25)	2/11 (18)
Discharged with gastronomy tube fiding	5/16 (31)	3/11 (27)
Outcome at 12 months after treatment		
Death	7/17 (41)	4/12 (33)
Severe disability	6/10 (60)	4/8 (50)
Death or severe disability	13/17 (76)	8/12 (66)
Neuromotor development delay	1/17 (6)	0/12 (0)
Survivors without disability	3/17 (18)	4/12 (33)
BSID-III composite score		
Cognitive	73.5 ±19.7	75.8 ±22.8
Language	72.4 ±23.7	74.3 ±25.0
Motor	68.2 ±23.9	68.5 ±24.0

TABLE 3. Adverse events for each type of cooling

Adverse events	SHC (n=17) n(%)	WBC (n=12) n(%)
Hypotension	12(70)	7 (58)
Bradycardia	1 (8)	0
Trombocyte count <100000 µL	10 (59)	3 (25)
Abnormal coagulation test	7 (41)	4 (33)
Abnormal renal function	5 (29)	4 (33)
Hyponatremia	9 (53)	5 (42)
Hypokalemia	5 (29)	3 (25)
Elevation of liver enzymes	11 (65)	6 (50)
Positive sepsis culture	2 (12)	1 (8)
Edema of scalp	1 (8)	0
Hypocalcemia	10 (59)	9 (75)
Persistent pulmonay hypertension	0	1 (8)
Air leak in lungs	0	1 (8)
Invasive mechanical ventilation during the period of cooling	16 (94)	11 (92)

nates with HIE. But these results require confirmation in further studies.

D) In another retrospective study on 66 neonates, Goenka A. 2020 et. al. [34] searched for significant differences after TH in terms of EEG and brain MRI appearance in neonates treated with either SHC (n = 22) or WBC (n = 44). They highlighted more severe damage to the CNS in the case of newborns treated with SHC. A higher percentage of newborns with severe EEG changes was observed among newborns treated with SHC, compared to the group treated with WBC. Basal ganglia and thalamus lesions were also seen on MRI images more frequently among infants treated with SHC compared with those treated with WBC. After the interpretation of the MRI images, statistically significant data could also be extracted. Lesions at the level of the basal ganglia and thalamus, as well as at the level of the cortex, without hemorrhage, were more frequent among newborns treated with SHC, compared to WBC (26% vs 7% p = 0.04). Also, the percentage of newborns without signs of HIE or CNS infarct/thrombosis, on brain MRI, is significantly higher for the patients treated with WBC, compared to SHC (67% vs 37%, p = 0, 0287).

TABLE 4. Hospital Course and Status at Discharge. Analysis of drug and blood components administration in the first week of life

	SHC (51)	WBC (57)	p-value
Respiratory support No (%) mean (days) (±SD)[a]	4.8 (±3.6)	6.0 (±6.6)	0.37
Noninvasive support [days]mean (days) (±SD)[aa]	0.7 (±1.3)	1.5 (±3.6)	0.26
Oxygen therapy [days] mean (days) (±SD)	5.6 (±7.6)	4.5 (±3.8)	0.47
Thrombocytopenia 100000 microliter (µL)	23	12	
Number; (%)	45.1	45.1	0.93
RBC transfusion (No; No of patients)	10/6	7/5	
No/patient	0.2	0.28	0.46
FFP transfusion (No; No of patients)	20/12	24/13	
No/all patients	0.39	0.89	0.36
Anticonvulsant administration (No of patients)	40	24	0.94
No of dose/all patients	141/2.8	80/2.9	
Antibiotic therapy [days] mean (±SD)	14.5 (±7.6)	13.1 (±6.8)	0.43
Full enteral feeding	14.5 (±5.9)	14.7 (±5.1)	0.92
Oral feeding (sucking) [days] mean (±SD)	16.7 (±10.2)	14.3 (±5.4)	0.37
Age at discharge/ DOL mean (±SD)	27.26 (±13.0)	21.91 (±11.3)	0.09
Death during hospital stay n (%)	3 (6.0)	2 (8.3)	0.71

The main limitation of the study is represented by the fact that it is a retrospective study, thus the division of patients according to the treatment method was not randomized, and the data collected may be flawed.

E) A prospective study published by Çelik Y. 2015 [35] included 54 newborns divided into 4 groups, after applying the exclusion criteria: SHC (n = 14), WBC (n = 10), mild HIE that did not meet the criteria for HT (n = 7) and a control group, without HIE (n = 9). This study wanted to see if there is a different effect that those two methods of HT have on certain biological markers.

TABLE 5. Frequency and type of MRI background abnormalities for SHC and WBC groups

MRI categories	SHC (19/22)	WBC (43/44)	p-Value
Basal ganglia - thalamus and cortex pattern with hemorrhagic lesion	1/19 (5%)	1/43 (2%)	0.52
Basal ganglia - thalamus and cortex lesion with no hemorrhage	5/19 (26%)	3/43 (7%)	0.04
Basal ganglia - thalamus lesion	3/19 (16%)	4/43 (9%)	0.42
Watershed or subcortical white matter lesion	1/19 (5%)	3/43 (7%)	0.76
Perinatal arterial ischemis stroke, perinatal hemorrhagic stroke, and sinovenous thrombosis	2/19 (11%)	3/43 (7%)	0.68
No signs of HIE or infarct/ thrombosis	7/19 (37%)	29/43 (67%)	0.0287

TABLE 6. Biomarker levels at 72 h

Biomarkers	SHC group (n=14)	WBC group (n=10)
IL-6 (pg mL^{-1})	64.2[a] (30.4-118.0)	43.0[a] (33.1-416.0)
IL-1β (pg mL^{-1})	2.2 (2.0-2.3)	2.2 (2.1-2.6)
TNF-α (pg mL^{-1})	19.5 (12.5-41.7)	17.0 (13.3-25.3)
NSE (μg L^{-1})	0.51 (0.38-0.74)	0.57 (0.38-1.70)
S100B (ng/ml)	0.08 (0.07-0.15)	0.10 (0.06-0.15)
S100 (ng L^{-1})	2.9 (0.5-15.5)	9.5 (0.3-29.8)
CKBB (ng mL^{-1})	1.0 (0.6-1.7)	0.8 (0.5-1.5)
L/C ratio	0.08 (0.04-0.27)	0.06 (0.04-0.16)

The levels of all biological markers investigated at 6 hours (serum IL-1β, TNF-α, NSE, CKBB and S100 protein) were similar in both groups of patients treated by SHC or WBC. The IL-6 level at 6 hours was significantly higher among patients treated with SHC and WBC compared to the control group. Also, the S100 protein level at 6 hours was significantly higher among TH-treated patients compared to the control group. The level of urinary lactate/creatinine ratio (L/C) at 6 hours was significantly higher than in the mild HIE group, as well as compared to the control group.

IL-6 level at 72 hours was similar in the SHC and WBC groups and was significantly higher than in the mild HIE group and the control group, without HIE.

By 12 months of age, in the group of neonates treated with SHC (n = 14), 5 had died, 5 had severe disability, 1 had neuromotor retardation, and 3 had no disability. In the group of newborns treated by WBC (n = 10) 5 patients died, 2 had a severe form of disability and 3 had no disability.

The 6- and 72-hour level of IL-6 and the urinary L/C ratio, among neonates with moderate and severe HIE who died, had severe disability and those who had neuromotor retardation at 12 months of life in patients, was significantly higher than in those who were alive without disability at 12 months of life. There were no other significant differences in other biological markers and prognosis at 12 months of life.

DISCUSSIONS

Systematic reviews published to date support that both modalities of therapeutic hypothermia cool CNS structures and have a similar neurodevelopmental prognosis among surviving neonates. Also, there are no significant differences in terms of short-term neurological prognosis, as well as the adverse effects that may occur in neonates with moderate or severe HIE treated with SHC or WBC; although some studies note the presence of more severe, statistically significant lesions among patients treated with SHC compared to those treated with WBC [1,26].

The physiological mechanism of this difference is not fully understood. But, most likely, given the animal studies that compared the two HT methods, the difference between the temperature present in the deep brain structures (thalamus and basal ganglia region) and the rest of the body plays an essential role. Thus the WBC method manages to maintain a constant low temperature throughout the body, including the central structures of the brain; compared to SHC, where there are significant temperature differences between basal ganglia temperature and the rest of the body [1,10].

At the same time, it is worth mentioning that although, following the extraction of data from clinical and paraclinical analyses, none of the methods proved to be significantly superior to the other; but WBC method has gained a lot in popularity compared to SHC. This fact can be explained if several aspects are taken into account. One of them is the much simpler process of initiating therapeutic hypothermia using the WBC method, as well as the ease with which constant °body temperatures of 33.5 C can be achieved using servo control. In the case of SHC, the cooling process occurs only at the level of the head, and the positioning of the leads, for monitoring by aEEG, further decreases the efficiency of maintaining a constant temperature at the level of the head; in the region where the derivations are present, the scalp no longer comes into direct contact with the cap that performs HT. As for the rest of the body, it is more difficult to achieve a constant low temperature compared to the WBC method. Also, in the case of SHC the aEEG leads should always be attached before fitting or changing the cap. This may lead to later initiation of therapeutic hypothermia compared to WBC, which is associated with a poorer prognosis [1,27,28,29].

Attempts are being made to find biological markers that can diagnose HIE and predict the severity of the lesions and the prognosis that the newborn may have. Many biological markers are studied in blood, urine and cerebrospinal fluid (CSF). Those that proved a degree of statistical significance are the serum value of IL-6, protein S100, CK-BB, as well as the urinary L/C ratio. A high value of these markers at 6 hours and at 72 hours predicts a worse prognosis and more severe CNS damage. So far, however, no significant difference has been discovered in terms of the values of biological markers, in relation to the TH method used (SHC vs WBC) [8,30,31].

Also, it is worth mentioning that the majority of newborns who meet the criteria for HT are not born in the tertiary center where the study is conducted. They are transferred via the neonatal transport unit (NTU) from a lower center to the tertiary one. Proper provision of the NTU to be able to initiate early TH or maintain an appropriate hypothermic environment with respiratory support and monitoring of aEEG and vital functions plays an essential role in improving the prognosis of newborns with moderate and severe HIE [21,25].

Prospective studies on a much larger scale are needed to track the adverse effects that the two TH methods may have on patients, as well as long-term neurological and cognitive prognosis.

CONCLUSIONS

There is evidence that TH is beneficial for term and near-term (VG > 35 weeks) neonates with HIE. Cooling reduces mortality without increasing the risk of developing a major neuromotor deficit in survivors. Also, the benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects. Hypothermia should be instituted in term or near-term neonates (VG > 35 weeks) with moderate to severe HIE if diagnosed before 6 hours of life. Prospective randomized clinical trials containing as large a number of patients as possible and evaluating both methods of HT (SHC vs WBC) are needed to determine the appropriate cooling techniques, including improving patient selection, duration of cooling, method of delivery HT as well as demonstrating the effectiveness of substances with an adjuvant role. Thus we will gain a better understanding of this treatment modality in HIE. Because, up to this point, many data are not statistically relevant.

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