Therapeutic Hypothermia for Asphyxiated Newborns: Experience of an Israeli Tertiary Center

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ABSTRACT: **Background:** Major advances in the treatment of perinatal asphyxial-hypoxic ischemic encephalopathy (PA-HIE) followed the translation of hypothermia animal studies into successful randomized controlled clinical trials that substantially influenced the current standard of care.

Objectives: To present our preliminary experience with the first cases of clinical application of therapeutic hypothermia for PA-HIE in what we believe is the first report on non-experimental hypothermia for PA-HIE from Israel.

Methods: We reviewed the medical records, imaging scans, electroencephalograms and outcome data of the six identified asphyxiated newborns who were managed with hypothermia in our services in 2008–2009.

Results: All asphyxiated newborns required resuscitation and were encephalopathic. Systemic hypothermia (33.5ºC) was begun at a median age of 4.2 hours of life (range 2.5–6 hours) and continued for 3 days. All six infants showed a significantly depressed amplitude integrated electroencephalography background, and five had electrographic seizures. One infant died (16%) after 3.5 days. Major complications included fat necrosis and hypercalcemia (n=1), pneumothorax (n=1), and meconium aspiration syndrome (n=2). None of the infants developed major bleeding. Neurodevelopmental follow-up of the five surviving infants at median age 7.2 months (4.1–18.5 months) revealed developmental delays (Battelle screening), with their motor scores ranging from -1 to +1 standard deviation (Bayley scale). None developed feeding problems, oculomotor abnormalities, spasticity or seizures.

Conclusions: Our preliminary experience with this novel modality in a large Tel Aviv neonatal service is consistent with the clinical findings of published trials.

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KEY WORDS: asphyxia, hypothermia, hypoxic ischemic encephalopathy, term infant, fat necrosis

Perinatal asphyxial hypoxic ischemic encephalopathy is an important cause of neonatal morbidity and mortality and long-term neurological disabilities, leading to a significant burden on society [1,2]. In developed countries, the incidence of PA-HIE is 1 to 2 in 1000 live births [3]. Between 10% and 15% of affected infants will die during the neonatal period, accounting for approximately one-fourth of the four million annual global neonatal deaths in the United States. [4]. The combined hemodynamic, respiratory, renal, gastrointestinal and coagulation systems of asphyxiated infants are affected, and the infants may present with various degrees of encephalopathy, seizures and feeding problems, depending on the extent of cerebral damage [1]. Between 25% and 45% of survivors develop neurodevelopmental handicaps in the form of cerebral palsy, mental retardation, visual or hearing deficit, learning and behavioral disability, or epilepsy [1-3].

Pathological and imaging investigations have clarified the primary cellular injury occurring after asphyxia, as well as the ensuing secondary damage that is the target for preventive interventions [5]. The ongoing search for a clinically valid neuroprotective method to improve the outcome of these affected infants finally led to the translation of hypothermia achievements in animal studies into successful clinical trials [6]. Hypothermia, both systemic and selective head cooling, has shown promise in numerous studies on asphyxiated infants [7-11]. The possible mechanisms responsible for these positive results include reduced neuronal metabolic demand, reduced cytotoxin accumulation, and prevention of apoptosis during secondary energy failure [3,12].

Although doubts have been raised about the true value of hypothermia in this setting [13], hypothermia is the only neuroprotective treatment among all the proposed interventions for PA-HIE that has shown benefit in several randomized controlled clinical trials. As a result, most centers worldwide have begun to use this novel approach on a non-experimental clinical basis.

In Israel, experimental hypothermia was first performed on four asphyxiated infants in the Soroka Medical Center (Beer Sheva, Israel) as part of the international TOBY trial [9]. Therapeutic hypothermia as a standard of care treatment was first introduced in our department at the Tel Aviv

PA-HIE = perinatal asphyxial–hypoxic ischemic encephalopathy

Sourasky Medical Center in 2008. We now describe this novel program and summarize our preliminary experience and the outcomes of the first infants treated with non-experimental therapeutic hypothermia for PA-HIE.

PATIENTS AND METHODS

The data for this retrospective study were retrieved from an electronic search of the Lis Maternity Hospital databases at the Tel Aviv Sourasky Medical Center from June 2008 to December 2009. The search words were "perinatal asphyxia," "hypoxic ischemic encephalopathy" and "hypothermia." We reviewed the medical records for specific demographic, maternal and antenatal, labor and intrapartum, and early postnatal data for each infant. Data were collected from the placental pathology reports for the presence of chorioamnionitis or any other abnormality. Neonatal cranial ultrasound (GE vivid-I), magnetic resonance imaging (GE Medical Systems), amplitude integrated electroencephalography (Olympic CFM 6000), and routine conventional electroencephalography (VIASYS healthcare) studies were reviewed. In addition, survival rate, neonatal clinical course, medical complications, and neurodevelopmental outcome of all survivors were documented. This study was approved by the institutional review board of Tel Aviv Sourasky Medical Center.

SELECTION CRITERIA FOR THERAPEUTIC HYPOTHERMIA

- Gestational age > 36 weeks and birth weight > 2000 g
- At least one of the following signs of fetal distress or history of acute perinatal event: severe fetal heart rate abnormality (variable or late decelerations), abruption placenta, cord prolapse, cord pH < 7.0, or base deficit > 16 mEq/L
- Evidence of neonatal distress as evidenced by at least one of the following: 10 minute Apgar score < 5, postnatal blood gas pH < 7.0 at < 1 hour or base deficit > 16 mEq/L, or continued need for ventilation for at least 10 minutes following birth.
- Evidence of moderate-to-severe neonatal encephalopathy according to criteria modified from Sarnat and Sarnat [14], including altered state of consciousness (lethargy, stupor or coma) with at least one of the following: hypotonia, abnormal reflexes (including oculomotor or pupillary abnormalities), absent or weak sucking, or clinical seizures.
- Abnormal aEEG with a minimum of 20 minutes of recording consisting of one of the following: upper margin < 10 μV (severe), upper margin > 10 μV and lower margin < 5 μV (moderate), or seizures identified by aEEG.

EXCLUSION CRITERIA

- Normal initial aEEG tracings, i.e., a lower margin > 5 μV and no seizures
- It was not possible to initiate cooling by 6 hours of age
- Severe congenital anomaly
- Severe bacterial or viral systemic or central nervous system infection
- Bleeding diathesis or major intracranial hemorrhage.

THE COOLING AND REWARMING PROCEDURE

Therapeutic hypothermia was introduced within 6 hours of birth. Infants were placed on the hypothermia blanket (CritiCool unit, MTRE Advanced Technologies, Israel) [15] set to an automatic control mode at 33.5°C for the rectal and skin probe. The infants were repositioned every 2 hours and remained on the hypothermia blanket for 72 hours. They were periodically monitored for their cardiorespiratory status, arterial blood gases, fluid and electrolyte balance, and liver, renal and coagulation functions. In addition, empiric antibiotics were given for a minimum of 72 hours after a routine sepsis workup. At the end of 72 hours of hypothermia, the automatic control was adjusted by an increase of 0.5°C every 2 hours until the temperature reached 36.5°C for the duration of one hour.

All infants were continuously monitored with aEEG, starting from admission to the neonatal unit and lasting for approximately 4 days, i.e., until 24 hours of rewarming had elapsed. Clinical and electrographic seizures were managed by phenobarbital and phenytoin as first- and second-line treatment, respectively [16]. The first CUS was performed before or soon after commencing hypothermia, and a follow-up CUS was performed after rewarming and repeated as indicated. Finally, a conventional electroencephalogram was performed and, when feasible, brain magnetic resonance imaging. Following their discharge from hospital, the infants were followed at the neonatal neurology outpatient clinic where the following were carried out:

- A comprehensive neurological examination that included assessment of neuromotor function (deep tendon reflexes, muscle tone, muscle strength), cranial nerves, and sensation
- A motor scale of the Bayley Scales of Infant Development II (comprising both fine and growth motor skills) from which the psychomotor developmental index was derived [17]
- **A** developmental screening of the Battelle developmental inventory (BDI-2) that included personal social, adaptive, motor, communication, and cognitive domains. A total screening score was then derived from which a developmental age was recorded [18].

RESULTS

Six asphyxiated term infants were managed with whole-body hypothermia in our center during the period 2008–2009.

aEEG = amplitude integrated electroencephalography

CUS = neonatal cranial ultrasound

Table 1. Demographic and intrapartum characteristics of the study group

Patient	1	2	3	4	5	6*
Gender	F	M	F	F	M	M
GA (wks)	40	41	40	40	40	37
Birth weight (g)	2575	4200	3456	3580	3360	2740
FHR	Abnormal	Abnormal	Normal	Abnormal	Abnormal	Abnormal
Maternal complications	–	PROM, GBS infection	–	Fever	Dyspnea, confusion	–
Meconium-stained amniotic fluid	Yes	Yes	Yes	No	Yes	No
Apgar scores at 1'/5'/10'/15'	2/4/5/7	0/0/0/5	1/2	1/3/4/4	2/5/7	0/0/6
Resuscitation	CPR	CPR	PR	PR	PR	CPR
Cord pH	6.91	6.76	6.7	6.8	6.75	6.7
Age at onset of hypothermia	6 hr	3 hr	5 hr	2.5 hr	6 hr	2.5 hr
Placental pathology	Fibrous and hyaline deposit	Chorioamnionitis, early vasculitis, calcifications	–	Chorioamnionitis	Funisitis, thrombus, calcifications	Funisitis

*Expired 3.5 days after birth

F = female, M = male, GA = gestational age, FHR = fetal heart rate, PROM = premature rupture of membranes, GBS = group B *Streptococcus*, CPR = cardiorespiratory resuscitation, PR = pulmonary resuscitation (intubation and ventilation)

Table 2. Neonatal outcome

Patient	1	2	3	4	5	6
Sarnat HIE grade	II	III	II	II	II	III
Liver transaminases	Elevated	Elevated	Elevated	Elevated	Elevated	Elevated
Creatinine	Elevated	Elevated	Elevated	Elevated	Normal	Elevated
Duration of ventilatory support	4 days	3 days	7 days	2 days	1 day	3 days
Duration of Pressor support	5 days	3.5 days	3 days	No	no	1 day
Major events	MAS	Meningitis, fat necrosis, hypercalcemia	MAS, bilateral pneumothorax	–	–	Death
Clinical seizures	No	Yes	Yes	Yes	Yes	No
Electrographic seizures (aEEG)	Yes	Yes	Yes	Yes	No	Yes
Background activity (aEEG)	Discontinuous	Isoelectric	Isoelectric	Burst suppression	Discontinuous	Burst suppression
Follow-up cEEG	normal (day 7)	Normal (day 7)	Normal (day 9)	Normal (day 7)	Normal (day-9)	–
CUS findings*	GW, PV, TH	GW, PV, IVH	PV, GW	GW, PV, TH	PV, TH, BG	GW, PV, TH
MRI findings†	BG, TH, WM, CR (day 7)	WM, IVH, PLIC (day 47)	BG, TH, BS, PLIC, WM (day 22)	TH, BG, PLIC, IVH (day 12)	–	–
Age at discharge (days)	12	21	10	14	16	–

HIE = hypoxic ischemic encephalopathy, aEEG = amplitude integrated electroencephalography, cEEG = conventional electroencephalography, MAS = meconium aspiration syndrome

*Cranial ultrasound findings included combinations of the following: loss of gray white matter differentiation (GW), intraventricular hemorrhage – mild severity (IVH), and hyperechogenicity of the PV (periventricular), thalamus (TH), and basal ganglia (BG) regions.

†Magnetic resonance imaging findings included combinations of the following: abnormal signal intensity on one or more of sequences (T1, T2, diffusion) of the cerebral cortex (CR), white matter (WM), posterior limb of internal capsule (PLIC), thalamus (TH), and basal ganglia (BG)

One infant had been transferred from another hospital for treatment 5 hours after birth. All infants showed evidence of intrapartum asphyxia, required resuscitation, and had evidence of early neonatal hypoxic ischemic encephalopathy [Table 1]. Hypothermia was commenced at a median age of 4.2 hours (range 2.5–6 hours). All infants had significant background aEEG abnormalities, and five also had electrographic seizures. Imaging abnormalities involving the basal ganglia, thalamus and white matter were detected on the CUS and/or MRI in all subjects [Table 2]. One infant (patient #6) who suffered from severe asphyxia and cardiopulmonary decompensation died at the age of 3.5 days. One infant (patient #2) developed fat necrosis and hypercalcemia. He also had a culture-negative meningitis, presumed to be secondary to group B *Streptococcus* transmitted from maternal infection. Two patients suffered from meconium aspiration syndrome,

Table 3. Neurodevelopmental outcome

Patient	1	2	3	4	5	6*
Age at examination (mos)	6.6	7.5	7.2	4.1	18.5	–
Neuromotor	Normal	Normal	Normal	Hypotonia(axial)	Normal	–
Oculomotor	Normal	Normal	Normal	Normal	Normal	–
Seizures	No	No	No	No	No	–
Feeding	Normal	Normal	Normal	Normal	Normal	–
PDI scores	94	91	–	86	107	–
Development age (mo)†	4	5	5	3	15	–

*Expired 3.5 days after birth

†Calculated from the Battelle developmental inventory (BDI-II) screening test

PDI = Psychomotor Development Index (the motor scale of the Bayley Scales of Infant Development-II standardized to have a mean of 100 and a standard deviation of 16)

and one of them developed bilateral pneumothoraces [Table 2]. None of the infants had a bleeding episode, but they all had asymptomatic prolonged coagulation and/or thrombocytopenia on laboratory workup. Prolonged coagulation was detected in four infants before beginning hypothermia and in one infant after the second day of hypothermia. Three infants were treated with fresh frozen plasma and one of them required cryoprecipitate. Three infants had thrombocytopenia, one of whom required platelet transfusions.

The neurodevelopmental follow-up of the five surviving infants at a median age of 7.2 months (4.1–18.5 months) revealed a normal neuromotor assessment in four infants, and normal oculomotor function and no feeding difficulties in all five infants. Hearing and visual behaviors were clinically normal in all five infants; however, formal visual and hearing tests were not available. All these infants showed developmental delays, their PDI scores ranged from -1 to +1 standard deviation, and none had developed seizures [Table 3]. They had all been successfully weaned from antiepileptic medications.

DISCUSSION

In 2005, a National Institute of Child Health and Human Development workshop summarized as follows: "although hypothermia appears to be a potentially promising therapy for HIE, long-term efficacy and safety are yet to be established" [19]. A few months later, the American Academy of Pediatrics Committee on the Fetus and Newborn commented that therapeutic hypothermia "should be considered investigational until the short-term safety and efficacy have been confirmed in the additional human trials underway" [20]. By 2007, data accumulated from additional clinical trials and a meta-analysis of eight trials showed that hypothermia is remarkably safe and significantly improves the outcome for many asphyxiated infants [3,21,22]. As a result, most centers worldwide have begun to use therapeutic hypothermia on a non-experimental clinical basis, and it was suggested by some authors that further randomized controlled trials would be unethical [13,21].

We present here our preliminary experience with the first six cases of therapeutic hypothermia for PA-HIE in a tertiary medical center in Israel. This program was a joint collaboration between neonatologists and pediatric neurologists. We determined eligibility for hypothermia using strict inclusion and exclusion criteria, based on clinical and aEEG guidelines published by the large trials [9,10]. All the infants we describe fulfilled those criteria, substantiating their diagnosis of PA-HIE grades II or III. Electrographic seizures were recorded in five patients, prompting a more strict anticonvulsive management for them. The cooling procedure was relatively simple to operate and uneventful for five patients. Patient #2 developed subcutaneous fat necrosis and hypercalcemia; this disorder had previously been reported in association with perinatal asphyxia [23], but hypothermia and skin pressure cannot be ruled out as additional etiopathogenetic factors, as was previously described by Wiadrowski and Marshman [24].

None of our study infants developed significant systemic or intracranial hemorrhage; however, they all showed prolonged coagulation time and/or thrombocytopenia, and three required specific treatment. Given the known risks for impaired coagulation after asphyxia, concerns were raised that hypothermia could worsen coagulation function in asphyxiated infants. Current data from the large hypothermia trials, however, suggested that the risk for prolonged coagulation or thrombocytopenia and significant bleeding is only slightly but not significantly increased by hypothermia [9-11]. Nonetheless, it is recommended that platelet and coagulation function be rigorously monitored in these infants.

A meta-analysis of the published large trials [3] confirmed the effectiveness of hypothermia treatment, with an overall reduction in rates of death from 33% to 24% (relative risk -0.74, confidence interval 95% 0.58–0.94) and moderate-to-severe neurodevelopmental disabilities from 42% to 28% (RR 0.65, CI 95% 0.48–0.87) for controls versus treatment groups. Sub-domain analysis revealed a reduction in rates of severe cerebral palsy (from 30% to 19%, RR 0.64, CI 95% 0.42–0.98), severe psychomotor delays (from 40% to 28%, RR 0.7, CI 95% 0.50–0.96), severe cognitive delays (from 39% to 27%, RR 0.69, CI 95% 0.50–0.96), severe visual deficits (from 15% to 9%, RR 0.56, CI 95% 0.30–1.07), and epilepsy (from 15% to 13%, RR 0.85, CI 95% 0.42–1.72) [3]. The accumulating evidence from this meta-analysis

PDI = psychomotor developmental index

RR = relative risk

CI = confidence interval

demonstrated potential prevention of death or severe disability in 1200 neonates per year in the United States, and the authors recommended hypothermia for the treatment of PA-HIE within the first 6 hours after birth, especially in infants with moderate encephalopathy [3]. In parallel with these neurodevelopmental advantages, a recent MRI study showed that therapeutic hypothermia is associated with decreased brain tissue injury in infants with PA-HIE [25]. The preliminary data of our first therapeutic hypothermia cases, particularly those pertaining to the neonatal course, are generally compatible with these published data. Our outcome evaluation revealed developmental delays in all survivors. However, despite the delays, the individual range of outcomes, including normal feeding, absence of seizures, and the relatively preserved gross motor scores without evidence of spasticity, are all reassuring and different from the expected clinical development in non-cooled PA-HIE survivors. Yet, the small sample size and relatively short follow-up preclude any in-depth comparison of our data to the published figures.

CONCLUSIONS

We describe our initial clinical experience with therapeutic hypothermia for PA-HIE in a tertiary medical center. We believe this to be the first report on non-experimental hypothermia from Israel. Our preliminary experience with this novel modality is in concordance with the efficiency, safety and neonatal profile described in published trials. This neuroprotective program is made possible by the cooperative efforts of neonatologists and pediatric neurologists. We recommend the establishment of an Israeli national registry of all PA-HIE cases in order to facilitate further research on unresolved questions, such as best timing and degree of hypothermia, role of aEEG and biomarkers for better selection of ideal candidates, long-term safety outcomes, and potential adjunctive neuroprotective drugs for enhancing this novel therapy.

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"The most beautiful thing we can experience is the mysterious. It is the source of all true art and science"

Albert Einstein (1879-1955)