



Therapeutic Hypothermia in Asphyxiated Neonates with Hypoxic-ischemic Encephalopathy: A single-center Experience from its First Application in Saudi Arabia (Research Article)

Authors

Najia Al Hojaili*¹, Hatem Alomari¹, Attia Alzahrani¹, Abdallah Kan¹

Rasha Mohammad

¹Department of Paediatrics, Maternity and Children's Hospital, Makkah, Kingdom of Saudi Arabia

Corresponding Author*

Dr Najia Al Hojaili

Consultant Neonatologist, MOH, B O pox 8981, Makkah Al-Mokarramah Saudi Arabia

Email: najoo_n1@yahoo.com, Mobile: 0569754397

Abstract

Background/ Objective: *Therapeutic hypothermia has become an accepted therapy in asphyxiated newborns with evidence of moderate to severe hypoxic-ischemic encephalopathy. In this study, it has been described our new experience with the whole body cooling treatment method in asphyxiated neonates. To our knowledge, this is the first relevant report in Saudi Arabia.*

Methods: *The medical records of all asphyxiated neonates treated with therapeutic hypothermia in Makkah Maternity children hospital between 2013-2015 were retrospectively reviewed. We recorded data related to neonatal-perinatal characteristics, total body cooling method was performed and outcomes.*

Results: *One hundred and forty asphyxiated neonates [median gestational age 38 weeks] received total body cooling (rectal temperature 33.5 ± 0.5 °C for 72 hours followed by slow re-warming) during the study period for moderate and severe hypoxic-ischemic encephalopathy. All neonates were depressed upon delivery with median Apgar scores 6 at 10 minutes. Therapeutic hypothermia was initiated at the median age of 6 hours after birth. On follow-up after our cooling method, neurodevelopment outcome was normal in 107 and 83 cases, depending on the evidence of computerized axial tomography (CAT) scan and the absence of clinical seizures after our cooling treatment method.*

Conclusions: *Our initial experience with total body cooling treatment method supports its beneficial effect as safe and effective in asphyxiated newborns. This treatment should be offered in all centers involved in the care of such neonates using our simple method.*

Keywords: *neonatal encephalopathy, neonatal care, perinatal asphyxia, total body cooling method, Saudi Arabia.*

Introduction

Hypoxic-ischemic encephalopathy (HIE) is a risk manifestation of perinatal asphyxia. It has been reported that 1-5 term neonates/1000 live births suffer perinatal asphyxia in developed countries [1,2]. In developing countries, the prevalence of perinatal asphyxia is considerably higher accounting for the one-fourth of neonatal deaths [3]. However, even in countries with sophisticated health care systems, asphyxiated neonates undertaken moderate to severe HIE are at significantly increased risk for severe handicap or death with important social-economic outcome in leavings [4,5]. These awful results are associated with the lack of any effective neuroprotective treatment following perinatal asphyxia. The clinical management of which survivors is mainly supportive caring until recently.

Brain injury and neuronal damage in acute hypoxia-ischemia is biphasic. At the beginning, primary energy failure process is occurred due to the consumption of high energy compounds such as adenosine triphosphate and phosphocreatine. This followed by a latent phase ~ 6 hours to make reperfusion for the ischemic brain. This may lead to complete recovery. But, in severe insults after 6 – 15 hours secondary energy failure will be the result. Also, late apoptotic cell death after the acute asphyctic event may be observed between 3 – 10 days [6,7]. Nevertheless, as shown in animal studies, there is still a "therapeutic window" - during the latent phase - where secondary neuronal injury could be prevented or reduced by brain cooling. This was confirmed in clinical trials. Indeed, most recent meta-analyses documented that therapeutic hypothermia - within the first 6 hours of life - in late preterm and term infants with moderate to severe encephalopathy and evidence of intrapartum asphyxia results in a significant reduction in mortality or major neurodevelopmental disability at the age of 18 months in survivors [8,9].

Because of the clinical benefits of therapeutic hypothermia, it is nowadays considered the golden standard of care in many developed countries. In

the United States, in 2013 it has been reported that 50% of the neonatal intensive care units (NICU) provide therapeutic hypothermia whereas 97% not offering this option and transfer eligible neonates to centers where cooling can be practiced [10]. In Europe, therapeutic hypothermia is already achieved in several countries as well. This because the participation of some medical centers in clinical trials such as: TOBY; in the United Kingdom, neo.nEURO; in Germany and in several European countries, while in others its use is expanding rapidly [11-15].

In Saudi Arabia; Makkah, our center is the first, and as far as we know the only center until recently (start of 2015), to apply therapeutic hypothermia for the treatment of asphyxiated neonates with HIE. This study aims at reporting our experience of two years of hypothermia therapy on asphyxiated newborns, demonstrating the characteristics of the newborn population undergoing this therapy way, birth conditions, clinical complications, adverse effects, features of body temperature control and follow-up during the stay in the neonatal unit. Moreover, as passive cooling technique was initially used in our center, this study may promote the application of hypothermia in asphyxiated neonates by other NICUs not offering this therapeutic option, yet, using our simple cooling method.

Human participants and recorded data

We retrospectively reviewed the medical records of all newly delivered asphyxiated babies and newborns admitted as cases of birth asphyxia at Maternity and Children hospitals in Makkah, treated with whole body cooling method in our level III NICU from 1st January 2013, till last January 2015. Parents of the asphyxiated neonates were informed about the importance of offering therapeutic hypothermia to their child with evidence of moderate to severe HIE. However, a written consent was not mandatory for treatment initiation in our institution as cooling is considered the standard of care [16].

Demographic parameters assessed included gestational age and birth sex. In addition, perinatal-neonatal characteristics variables as inborn neonates, mode of delivery, acute intrapartum events, Apgar scores at 10 minutes, neonatal resuscitation needed and blood gases within the 1st hour were evaluated. Severity of HIE as assessed prior to cooling according to Sarnat scale ⁽¹⁶⁾, time of cooling initiation after birth, adverse effects and interventions during cooling and outcome (survival, neurodevelopment outcome) were included as well. Data on computerized axial tomography (CAT) of the brain performed during the hospital stay were also reviewed. Interventions and adverse effects studied included invasive mechanical ventilation, persistent pulmonary hypertension of the neonate requiring inhaled nitric oxide, arterial hypotension and need for inotropes. Additionally, sinus bradycardia (heart rate <80 beats/min), acute renal failure (increase of serum creatinine \geq 0.3 mg/dL from previous value within 48 hours), disseminated intravascular coagulation, hyperglycemia, thrombocytopenia (platelet <100 x 10⁹/L) and early-onset sepsis (positive blood culture in the first 72 hours of life) were studied.

Inclusion and exclusion criteria for neonates cooling

All babies were selected and treated according to our local guidelines which were consistent with those used in clinical trials of therapeutic hypothermia. Briefly, newborn infants born at \geq 36 weeks gestation were eligible for treatment if they had evidence of acute perinatal asphyxia and of moderate to severe HIE taking into consideration Sarnat criteria ⁽¹⁷⁾. In addition, severe acidosis (pH \leq 7) combined either with Apgar scores \leq 5 or with continuing need of assisted ventilation were features to observe. Neonatal neurological sequel: hypotonia, coma and neurologic signs and symptoms of encephalopathy, i.e., the presence of postnatal seizures or clinical signs of encephalopathy were included as required characteristics for our

treatment method ⁽¹⁸⁾. Neonates less than 34 weeks gestation or birth weight <1,800 g, with severe congenital anomalies, known perinatal infection and severe bleeding were excluded from our cooling treatment method.

Total body cooling method and re-warming procedure

Our way for treatment was conducted for all eligible neonates after 6 hours of birthing in our center by active whole body cooling therapy procedure. Rectal temperature (core body temp.) was maintained with this cooling method at 33.5 ± 0.5 °C for 72 hours while re-warming took place gradually (0.5 °C/h) until the desired rectal temperature (36.5 °C) was reached. Briefly, all neonates were nursed in an open incubator, uncovered, naked, wearing diaper only during treatment, were given Morphine infusion to decrease pain and received standard neonatal care. Cold packs from the refrigerator (around 10°C) are wrapped in cotton towels, never in direct contact to skin, placed around the baby's body. The use of fans and/ or air conditioner could be considered depending on seasonal temperature depending on the ambient air temperature in the NICU. Continuous rectal temperature monitoring is used, insert rectal probe into the anus at 5 cm and fix it to the thigh. It is very important that the probe is inserted to this depth to accurately measure the core temperature. Rectal probe was connected to cable, temperature module, and monitor. Temperature alarm limits in the method was adjusted at 33.5°C (low) and 34.5°C (high) during cooling. Recording time of initiating active cooling and monitor rectal temperatures was performed every 15 min. If the rectal temperature drops below 34.5°C, remove all the cool packs and reassess temperature in 15 min. If the temperature continues to fall during the method, radiant warmer was set on manual and gradually adjust the heater output to maintain the temperature at 33.5-34.5°C. Because our aim is to achieve the target temperature range within 1 h, but more importantly, continue to manage airway,

breathing, and circulation in safe manners. Active cooling measures were reduced if the rectal temperature falls below 35°C, arterial oxygen tension (PaO₂) increased by more than 50% after the initiation of procedure. Active cooling measures were stopped when the rectal temperature falls below 34.5°C, the baby has persistent hypoxemia on 100% oxygen, there is life-threatening coagulopathy and if there is an arrhythmia requiring medical treatment to use re-warming procedure. After stopping active cooling, monitoring temperature every 30 min until it reaches 35°C. Then, resuming active cooling when the temperature reaches 35°C and the baby is clinically stable. After completion of 72 h of total body cooling, slow re-warming was achieved by stopping any active cooling strategies and gradually increasing the incubator temperature by 1°C to increase the rectal temperature to 36.5-37°C at the end of the procedure.

Statistical Analysis

Frequency distribution, chi-square and t-test analysis will be used to compare percentages of studied parameters among patients group participated in the study. The statistical analyses were performed using IBM SPSS Statistics v. 11.5 for Windows. p-value < 0.05 was used as the level of significance.

Results

During the study period, 140 neonates with median gestational age 38 weeks (36-40) and median birth weight 3,161 g (2,200-4,700) received therapeutic hypothermia for acute perinatal asphyxia and evidence of moderate to severe HIE. The majority of the patients were male (83.6 %). A spontaneous vaginal delivery (SVD) was performed in ~ 50% of the deliveries. ~ 39 % of births were breech and the remaining neonates were born by caesarian section. Mothers of the infants with median age 30 years (16 to 45), (2 %) had gestational hypertension and chronic hypertension. None of them had gestational diabetes mellitus or gestational coagulopathies.

Parity was variable in between mothers of asphyxiated infants ranging from zero to 13 children. All neonates were depressed upon delivery with median Apgar scores 6 at 10 minutes. The neurodevelopmental outcome as assessed by computerized axial tomography (CAT) scan findings and clinical seizures before hospital discharge to be normal for 107 (p = 0.036) and 83 (p = 0.43) neonates, respectively.

Discussion

In this study, we present our experience with therapeutic hypothermia when preformed for the management of asphyxiated neonates with moderate or severe HIE beyond the framework of clinical trials in a tertiary NICU of KSA. Our results are encouraging with respect to the feasibility, safety and beneficial effect of whole body cooling method in terms of survival and neurodevelopmental outcomes being consistent with the results of large clinical trials.

Although there were some reports showed that hypothermia was used successful to resuscitate newborns after delivery back in the 50s, it has emerged again as a promising therapeutic option in asphyxiated neonates with HIE only during the last two decades ^[6]. In the most important randomized clinical trials performed so far, selective head ^[19,20] or total body cooling ^[11,13,21] was applied using automated instruments designed to maintain target rectal temperature at 34-35°C and of 33-34°C, with the respective cooling modes. No superiority of either modality is supported by the existing evidence ^[9]. In this study, all the neonates were cooled using simple means as described above. It is our feeling that cold packs cooling method could be easily applied in centers with no or minimal experience in which an automated device is lacking, provided that the core body temperature is monitored to keep it in the target range. Infant Cooling Evaluation Collaboration (ICE study) clinical trial has reported that whole body cooling using low tech methods was safe and effective for HIE cases. Owing to its practicality and low cost, it is used by

several centers even in high resource countries [14,22,23]. Still, one should be aware of the highest variation of temperature with this cooling method [14].

All neonates in which cooling were performed in the present study had moderate to severe HIE and took part in according to the inclusion criteria reported above. Because we were in the early phase of the learning curve and the medical staff is reluctant in implementing therapeutic hypothermia, most probably there was a biased selection of the severely affected neonates. Interestingly, in other important clinical trials, most of the cooled neonates had moderate HIE as reported by researchers in the Neonatal Research Network of the National Institute of Child Health and Human Development, one of the National Institutes of Health (NICHD; neonatal network, 68%), ICE (57.3%) and China study group (41%) studies [20-22].

Interestingly, in the present study, all of the neonates participated survived to hospital discharge while no deaths present in neonates with HIE treated with our method. Hypothermia has been well documented to decrease mortality in asphyxiated neonates, but we could not know the survival of these babies if this intervention had not been applied. On the other hand, the good neurodevelopmental outcome as evaluated after our cooling method is encouraging. As evidenced by the most recent Cochrane meta-analysis, 8 asphyxiated neonates with moderate to severe encephalopathy would need to be cooled in order to prevent neurodevelopmental disability in 1 survivor [9]. In addition, it is worth noting that in this cohort of asphyxiated neonates, hypothermia was attempted beyond the "therapeutic window" of the first 6 hours of life, considered to be the optimal time period for neuroprotection [6-9]. Several factors may delay initiation of treatment as late recognition of eligible patients and/ or, need for transfer. Data analysis between December 2006 and July 2011 on the implementation-conduction of therapeutic hypothermia in the United Kingdom showed that

2.2 % of the neonates suffering asphyxial encephalopathy had cooling commenced more than 12 hours after birth [12]. Furthermore, in a retrospective review of neonates referred to a regional tertiary center in Canada, 44% of the patients had cooling initiated after 6 hours of age [24]. The efficacy of this intervention may be reduced when the treatment was attempted after 6 hours from delivery possibly explaining the poor neurodevelopmental outcome of some neonates with moderate and severe HIE analyzed in another studies (33). Ongoing studies on this issue by NICHD reported a term late hypothermia that could be expected to provide insights as to whether the later timely application of therapeutic hypothermia is beneficial [9]. Cooling during transport could be an alternative approach as initiation of effective hypothermia is achieved significantly earlier, but clinical protocols and devices for cooling in transport are essential to ensure safety and efficacy [23, 25].

Potential limitations of this study are the small number of studied neonates and it's retrospective type. As neonates in this cohort can be considered as small number and would be increased to a suitable number with the aid of a power calculation. However, data presented here are derived from a single center and, therefore, only a limited number of neonates could have been evaluated in a relative short time period, particularly with respect to long-term outcome. On the other hand, the retrospective analysis permits the detection of important clinical parameters which could allow further improvement in the clinical implementation of this novel therapeutic approach.

In conclusion, therapeutic hypothermia is considered to be the optimal care in asphyxiated neonates with evidence of moderate to severe HIE. This treatment method should be offered in a timely manner by all centers involved in the care of such neonates. Although high tech cooling using specific devices is preferable in terms of temperature stability, simple low tech cooling can be safe and effective to be applied. In all cases,

however, local protocols should be developed based on the existing skilled personal with international experience.

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