Published in final edited form as:
J Pediatr. 2010 September ; 157(3): 499–501.e1. doi:10.1016/j.jpeds.2010.04.011.

Therapeutic Hypothermia for Neonatal Encephalopathy and Extracorporeal Membrane Oxygenation

An Massaro, MD[1], **Khodayar Rais-Bahrami, MD**[1], **Taeun Chang, MD**[2], **Penny Glass, PhD**[3], **Billie Lou Short, MD**[1], and **Stephen Baumgart, MD**[1]

[1] Department of Neonatology, Children's National Medical Center

[2] Department of Neurology, Children's National Medical Center

[3] Department of Psychiatry and Behavioral Sciences, Children's National Medical Center

Abstract

This case series describes clinical management of five infants who received whole-body cooling during extracorporeal membrane oxygenation (ECMO). We maintained systemic hypothermia during ECMO with acceptable clinical outcomes.

Keywords

ECMO; hypoxia-ischemia; brain; newborn

Whole body cooling according to the NICHD protocol [1] has been used to treat encephalopathic newborns referred to the Children's National Medical Center NICU since May 2006. Modified Sarnat criteria are used to define moderate to severe encephalopathy needed for entry onto the whole-body hypothermia therapeutic protocol [1]. To date we have provided whole body cooling to 117 patients meeting these criteria. Children's National Medical Center ECMO criteria include persistent hypoxia (preductal SpO_2 <90 or PaO_2 < 50mmHg) or hemodynamic instability despite maximal medical support. We report a case series of 5 patients who met institutional cooling and ECMO criteria either simultaneously or sequentially in the past 3 years.

CASE SERIES

Five infants were treated with whole body cooling during ECMO life support between September 2006 and May 2009. Data were collected as part of an ongoing retrospective review of outcomes in our hypothermia-treated population. The need for study consent was waived by the Institutional Review Board.

Demographic and clinical characteristics of the 5 patients described in this report are summarized in Table I. All infants had histories of perinatal distress (non-reassuring fetal heart tracings) and were resuscitated at delivery for meconium aspiration. They met

Corresponding Author: An Massaro, MD, Children's National Medical Center, Division Neonatology, 3W-600, 111 Michigan Ave, NW, Washington, DC 20010-2970, Tel: 202-476-5225, Fax: 202-476-3459, anguyenm@cnmc.org.

The authors declare no conflicts of interest.

physiologic criteria for hypothermia with metabolic acidosis demonstrated from cord blood gas or arterial blood gas within one hour of birth (median pH 6.80, range 6.66–6.80, base deficit 17±9) and presented with severe clinical encephalopathy. The infants were initiated on the whole body hypothermia protocol upon arrival and were managed with mechanical ventilation and nitric oxide before developing worsening hypoxia requiring ECMO cannulation at a median age of 19 hours (range 7–64). One patient was managed with veno-venous (VV) ECMO (patient #3), and the remaining infants were treated with veno-arterial (VA) ECMO.

Cooling Method

Hypothermia was provided using the ECMO apparatus' blood warmer (Cincinnati Sub-Zero; Cincinnati, OH) as the primary implement for cooling. Infant core temperature using continuous esophageal thermometers was targeted at 33.5°C for 72 hours followed by rewarming over 6 hours by 0.5 °C per hour. Blood path temperature is monitored proximate to the arterial cannula (near the AV-bridge, and 122 cm distal to the heat exchanger (Medtronic Inc; Minneapolis, MN). In general, the blood path temperature is 1.5–2.0°C cooler than the set water bath water temperature of the servo-regulated blood warmer. Thus, the water bath temperature was set at 35°C (expecting this to achieve a blood path temperature close to 33.5°C). The baby was continued on the servo-regulated cooling blanket (Cincinnati Sub-Zero; Cincinnati, OH) set to automatically control to a target esophageal temperature of 33.5°C. Temperature variance for this method was <1.5% from the target temperature (Figure; available at www.jpeds.com).

Adverse Events

One patient developed transient bradycardia to 50–60 beats per minute when put on ECMO 60 hours after initiating cooling. Bradycardia resolved with rewarming, before weaning off ECMO, and the infant's pH and SvO_2 remained normal without any base deficit throughout this event. Three of the four remaining patients had mild sinus bradycardia (heart rate 80–100 bpm) noticed during cooling that did not require intervention. Four patients had hypotension requiring vasopressor support that was discontinued after stabilization on ECMO. Four patients had initial transient oliguria that resolved by day of life 4. All patients had some evidence of end-organ ischemia with either elevated liver or renal function tests (Table II; available at www.jpeds.com), although these studies normalized in all patients prior to discharge. Likewise, all patients demonstrated prolonged coagulation studies and thrombocytopenia during hypothermia. All five patients received platelet transfusions (median number during 72 hour cooling period=3, range 2–4), three patients received fresh frozen plasma (FFP) (median 2 transfusions, range 1–6) and two patients received a single cryoprecipitate transfusion. Three patients had evidence of pulmonary hemorrhage. Two were noted to be mild and resolved with increased peak end expiratory pressure on the ventilator. One patient had more significant bleeding that resolved after administration of FFP and platelets. Three patients had intracranial hemorrhage- one with a small choroid plexus hemorrhage and 2 with subdural and intraparenchymal hemorrhages.

Patient Outcomes

All 5 patients survived to hospital discharge (Table I). Three were developmentally age appropriate at follow-up (assessment interval ranged from 6 to 21 months). Patient #2 seen at 3 months was noted to have tone abnormalities, but was subsequently lost to follow-up. Patient #5 developed progressive hydrocephalus following discharge and had ventriculoperitoneal shunt placement. He was assessed at 5½ months and found to have significantly delayed motor and cognitive/play skills.

DISCUSSION

Hypothermia has been increasingly adopted since being demonstrated to reduce adverse outcome (i.e. death or neurodevelopmental impairment at 18 months) in infants with moderate to severe neonatal encephalopathy [1–3]. We report neonates treated with the established NICHD therapeutic hypothermia protocol [1] who also received ECMO life support. Although our experience is limited to whole body cooling, these findings may be generalizable to infants undergoing selective head cooling because adverse effect profiles appear to be similar between both cooling modalities [3]. It is known that intrauterine fetal distress and fetal asphyxia are associated with stimulation of intestinal peristalsis and relaxation of the anal sphincter resulting in premature passage of meconium in compromised fetuses [4]. Thus, it is not surprising that asphyxiated babies manifesting encephalopathy would also be at risk to develop meconium aspiration syndrome and hypoxic respiratory failure requiring ECMO. We report cases of infants who met defined criteria for entry into hypothermia before meeting institutional criteria for ECMO.

ECMO is a therapy that alone has adverse neurodevelopmental impact. Infants who are treated with ECMO in the neonatal period are at increased risk for cerebral palsy (10–20%), mental retardation (15%), hearing impairment (3–21%) and learning/behavioral problems (50%) [5–6]. These outcomes may be related to increased risk for hemorrhagic and nonhemorrhagic infarction resulting from cardiorespiratory instability pre-ECMO, and the neurologic risks during ECMO including ligation and cannulation of major vessels supplying the cerebral circulation, prolonged anticoagulation, and potential for thromboembolic phenomenon and inflammatory insults [6]. These observed risks have led to pilot studies reported by Ichiba and Horan evaluating the safety and feasibility of mild hypothermia as a neuroprotective strategy during ECMO [7–8]. Temperature was lowered from 37°C to 34°C and duration of cooling increased to a maximum of 48 hours in sequential groups of patients (total n=45 in two separate trials). They reported no bleeding or cardiac arrhythmia complications and no impact on platelet, complement, cytokine or coagulation profiles. These studies, in addition to the low rate of bleeding complications reported in the original NICHD trial [1], led to our institutional decision to complete 72 hours of hypothermia even if patients required ECMO support. We report the feasibility of providing hypothermia in conjunction with ECMO while utilizing greater depth and duration of cooling (33.5°C for 72 hours) than was used in the previous pilot studies. Utilizing the servo-regulated cooling blanket in conjunction with blood temperature regulation via the ECMO circuit allowed for maintenance of core temperature with little variance as demonstrated by continued esophageal temperature monitoring. This is essential for gauging and providing therapeutic effects.

It is acknowledged that this report, while demonstrating feasibility of providing therapeutic hypothermia during ECMO, does not provide a comprehensive assessment of the safety and efficacy of these combined therapies. Although the bleeding complications observed were not beyond what is routinely encountered during ECMO support, determined whether cooling may have affected this risk. Likewise, known adverse effects associated with cooling such as hypotension requiring vasopressor support and thrombocytopenia [3] are also frequently observed before and during ECMO. It is reasonable to counsel families that even though both therapies have been independently demonstrated to improve outcomes in specific clinical scenarios, the combination of these therapies is less certain. This report adds preliminary feasibility data for future randomized controlled trials (ongoing in UK and planned in US: co-principal investigators Seetha Shankaran and Beena Sood at Wayne State University) to evaluate therapeutic hypothermia for neuroprotection in infants requiring ECMO.

References

1. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole body hypothermia for neonates with hypoxic ischemic encephalopathy. N Engl J Med 2005;353:1574–84. [PubMed: 16221780]
2. Shankaran S, Pappas A, Laptook AR, McDonald SA, Ehrenkranz RA, Tyson JE, et al. Outcomes of safety and effectiveness in a multicenter, randomized controlled trial of whole-body hypothermia for neonatal hypoxic-ischemic encephalopathy. Pediatrics 2008;122:e791–8. [PubMed: 18829776]
3. Jacobs S, Hunt R, Tarnow-Mordi W, Inder T, Davis P. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev 2007:CD003311. [PubMed: 17943788]
4. Wiswell TE, Bent RC. Meconium staining and meconium aspiration syndrome. Ped Clin North Am 1993;40:955–981.
5. McNally H, Bennett CC, Elbourne D, Field DJ. United Kingdom collaborative randomized trial of neonatal extracorporeal membrane oxygenation: follow-up to age 7 years. Pediatrics 2006;117:e845–854. [PubMed: 16636114]
6. Short BL. The effect of extracorporeal life support on the brain: a focus on ECMO. Semin Perinatol 2005;29:45–50. [PubMed: 15921152]
7. Ichiba S, Killer HM, Firmin RK, Kotecha S, Edwards AD, Field D. Pilot investigation of hypothermia in neonates receiving extracorporeal membrane oxygenation. Arch Dis Child Fetal Neonatal Ed 2003;88:F128–133. [PubMed: 12598502]
8. Horan M, Ichiba S, Firmin RK, Killer HM, Edwards D, Azzopardi D, Hodge R, Kotecha S, Field D. A pilot investigation of mild hypothermia in neonates receiving extracorporeal membrane oxygenation (ECMO). J Pediatr 2004;144:301–308. [PubMed: 15001932]

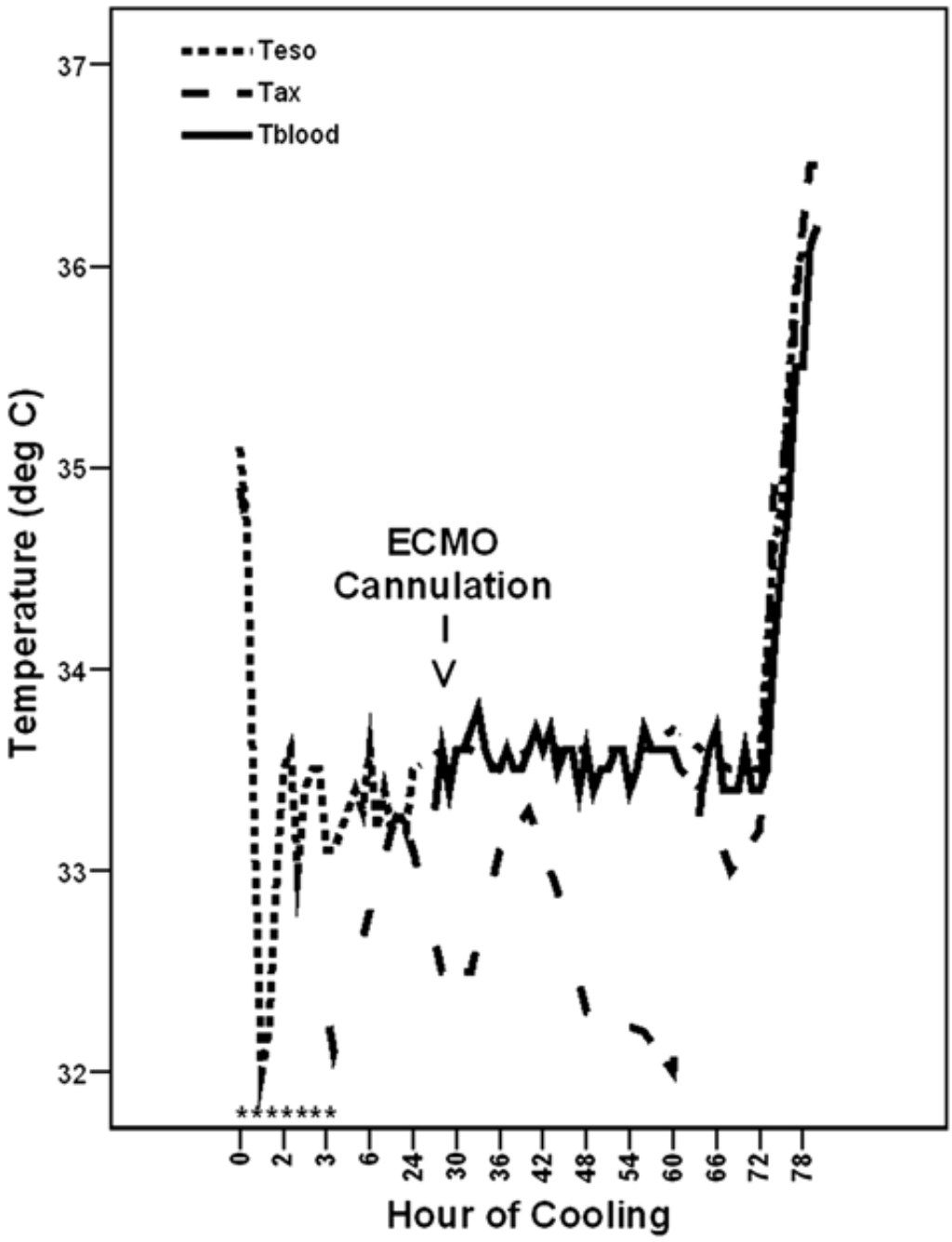

Figure 1.

Temperature using ECMO Circuit Combined with Cooling Blanket to maintain hypothermia on ECMO. Note variation in axillary temperature while continuous esophageal monitored temperature is tightly controlled and approximates blood temperature. **** Initial 4 hours of cooling are presented in larger scale to demonstrate initial overshoot to 32°C with induction of hypothermia. This is typically observed prior to equilibration [2] and captured when temperature is recorded every 15 minutes in the first 4 hours of hypothermia.

TABLE 1

Demographic and Clinical Characteristics of ECMO/Hypothermia Patients

Pt	GA (wks)	BW (kg)	Sex	Age at cooling (hours)	Age on ECMO (hours)	Initial pH	Base Deficit	1 Min Apgar	5 Min Apgar	Dx	ECMO days	LOS	EEG Seizures	Post ECMO MRI Findings (DOL)	OUTCOME (Assessment Age)
1	36	2.78	M	5:43	64:53	6.66	n/a	4	3	Chorio MAS	6	28	No	Normal (DOL 10)	MDI/PDI normal (21 months)
2	38	3.08	M	5:56	30:07	6.69	27	2	3	MAS	18	50	No	Choroid plexus hemorrhage (DOL 31)	Increased tone (3 mo, then LFU)
3	39	3.11	F	3:06	19:08	6.90	10	1	3	Chorio MAS	8	31	No	Normal (DOL 16)	MDI/PDI normal (6 mo)
4	39	3.15	F	4:15	13:12	6.80	10	4	5	MAS	8	22	Yes	Parietal/SDH, multifocal signal abnl (DOL 9)	MDI/PDI normal (9 mo)
5	40	3.84	M	4:55	7:08	6.80	22	4	7	MAS	11	45	No	Parietal/SDH, basal ganglia edema (DOL 16)	MDI/PDI <50 (5.5 mo)

GA = gestational age, BW = birthweight, Dx= diagnoses, LOS= length of stay, DOL= day of life, MAS = meconium aspiration, Chorio = maternal chorioamnionitis, CDH = congenital diaphragmatic hernia, SDH = subdural hemorrhage, MDI = Bayley Mental Developmental Index, PDI = Bayley Psychomotor Developmental Index, LFU = Lost to follow-up

Table 2

Laboratory Values During Hypothermia

	Median (range)
Peak Aspartate aminotransferase (units/L)	156 (76–272)
Peak Alanine transaminase (units/L)	47 (30–57)
Peak Blood Urea Nitrogen (mg/dL)	11 (6–21)
Peak Creatinine (mg/dL)	1.1 (1–1.2)
Lowest Platelet (K/mcL)	54 (31–118)
Lowest Fibrinogen (mg/dL)	124 (67–166)
Longest Prothrombin Time (sec)	28.5 (26–35.6)
Longest Partial Thromboplastin Time (sec)	52.9 (38–127)