Ethical perspectives in cooling for term infants with intrapartum asphyxia

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doi: 10.1111/j.1469-8749.2011.04178.x

Clinical neurosciences are presently in the midst of a paradigm shift from a descriptive approach to an interventional undertaking. This transition is built on an increased understanding of pathogenic mechanisms underlying acute neurological dysfunction, driven largely by advances in cellular biology and imaging. These advances have enabled the formulation of therapeutic interventions for acute potentially catastrophic events that can lead to a favourable outcome. In the adult context, the prototype is the use of tissue plasminogen activator (tPA) for stroke.[1] In infants, the prototype is the use of cooling in the setting of term born asphyxia.[2] It is to be expected that such a therapeutic advance applied to the severely compromised infant at the beginning of life would pose challenges to our ethical perspectives.

Intrapartum asphyxia in the term infant is a recognized and relatively frequent cause of neonatal neurological morbidity, manifesting itself through the occurrence of neonatal seizures and/or encephalopathy.[3] Aside from acute manifestations, it carries with its occurrence the risk of significant long-term sequelae which include such symptom complexes as cerebral palsy and/or intellectual disability.[4]

Both the treatment of intrapartum asphyxia and efforts at early prognostication have been hampered by the lack of an objective criterion standard for its recognition and definitive diagnosis. At present, clinicians rely on an expert-driven consensus approach, that includes both essential and supportive features.[5,6] Essential features include: (1) a moderate or severe neonatal encephalopathy; (2) an acidotic cord pH or early (first hour of life) infant blood gas pH; and (3) the absence of evidence for another plausible non-asphyxial etiology.[7] Supporting features include: (1) the occurrence of a sentinel event (e.g. cord prolapse, uterine rupture, abruptio placentae); (2) fetal heart rate pattern changes indicative of potential fetal compromise (e.g. late decelerations, persistent bradycardia, loss of beat to beat variability); (3) an APGAR score less than 6 at 5 minutes and beyond; (4) case-room resuscitative efforts (e.g. intubation, external cardiac massage, fluid boluses); (5) objective evidence of involvement of a non-central nervous organ system (e.g. renal, hepatic, cardiac); (6) electrographic (EEG-background attenuation, burst suppression pattern); or (7) imaging (e.g. selective neuronal necrosis, deep grey matter involvement, watershed infarcts) changes considered to be characteristic of asphyxia.[7] Left unclear at present is the number and spectrum of supportive features considered necessarily contributory to definitive diagnosis.

For term infants with intrapartum asphyxia, a broad range of potential outcomes are possible.[8] At the extremes, these include a lack of any overt limitations (i.e. normality) and death, with early death due to either the withdrawal of 'life essential' supportive care in the neonatal intensive care unit or to the later effects of sepsis, aspiration, or protracted seizures on a medically fragile child. Intermediate between these two extremes a whole host of outcomes may occur. At the severe level, this may consist of cerebral palsy (spastic quadriparetic, dyskinetic, or mixed) with significant functional limitations (e.g. gross motor, fine motor, speech/language). These functional limitations may leave the child immobile, unable to roll or sit, without purposeful hand use, and non-verbal. Such a child may be entirely dependant for all activities of daily living and require enteral tube feeding. Furthermore, comorbidities such as significant sensory impairments (e.g. blindness, deafness), intellectual disabilities, and orthopedic deformities (e.g. scoliosis) may occur.[9] Indeed for many children and their families, it is the functional limitations and comorbidities that are the major care burden and focus of caregiving efforts.[10] More recently, non-cerebral palsy outcomes of intrapartum asphyxia have been recognized to occur, complicating efforts at accuracy in early prognostication efforts.[8]

Outcome prediction in the setting of term intrapartum asphyxia is not yet an exact science.[11] Inter-individual resiliency reflecting variations in the individual response to acquired brain injury and neuroplasticity, together with a lack of objective quantifiable measurements of brain injury itself, hamper our efforts. This is further complicated by wide variations in access to available medical, rehabilitation, and societal resources that may act as outcome modifiers. Recognized predictors routinely used by clinicians include: (1) stratification of the severity of neonatal encephalopathy; (2) the temporal evolution in clinical status over the first week of life; (3) the presence of refractory neonatal seizures; (4) documentation of a burst-suppression EEG pattern; and (5) a qualitative impression of the severity of imaging changes.[12–18] Of these, the first two factors (i.e. the severity of neonatal encephalopathy and its temporal evolution over the first week of life), have traditionally held the greatest weight.[8,11] Indeed, it is felt that the infant with a mild encephalopathy will invariably have an outcome free of significant life compromising neurological sequelae, while those with a severe neonatal encephalopathy will either die or have significant neurological sequelae.[8] Outcomes appear to only be in doubt for the infant with a moderate neonatal encephalopathy.[8] Furthermore, an improvement in the severity of neonatal encephalopathy during the first week of life is felt to be indicative of reasonable hope for a good outcome.[11]

The landscape for this clinical situation was irrevocably changed in 2005 with the near simultaneous publication of two multi-centre and multi-national randomized controlled

trials.[19,20] Utilizing a rigorous prospective study design and employing two different methods of cooling (i.e. cool cap, total body), lowering core body temperature by three to four degrees Celsius for a duration of 72 hours beginning within 6 hours of asphyxial injury was shown to significantly impact on intermediate outcomes at 18 months of age. Careful subgroup analysis revealed a statistically significant demonstrated benefit for infants with a moderate neonatal encephalopathy with respect to moderate or severe disability (including cerebral palsy and intellectual disability) or death.[2] Subsequent meta-analysis of pooled data has noted that seven infants with intrapartum asphyxia need to be cooled for every child who actually benefits from this intervention in an objective manner.[21]

The results of these studies have led to the widespread establishment of regional cooling centres with the implementation of cooling algorithms for both case recognition and treatment intervention. Cooling has been the focus of extensive knowledge translation efforts directed at birthing centres and obstetrical units, and cooling has emerged both as a standard of care and a predicate upon which future therapeutic efforts for asphyxiated term infants will be based (i.e. 'cooling plus' strategies).[22]

For the clinician involved in the care of the asphyxiated term infant, extensive personal experience has led to the observation of change in both prediction and practice that has ethical implications. In the pre-cooling era, in the infant with a severe neonatal encephalopathy reflecting severe asphyxial compromise, efforts at prognostication would tend to occur on the second or third day of life. Utilizing early clinical, electrographic, and imaging markers of a high risk of significant sequelae, such an outcome would be predicted with reasonable certainty and communicated to parents. In such a context, parents would often elect for the withdrawal of ventilator support and the substantial cardiorespiratory compromise suffered by the infant would preclude independent respiration and early death within the neonatal intensive care unit would often result. In the post-cooling era, once cooling has been implemented on the first day of life, it is maintained for 72 hours. Only after the end of cooling, when an infant remains severely encephalopathic, would prognostication efforts be undertaken. Thus an adverse outcome may be predicted with reasonable certainty and communicated on the fourth or fifth day of life at which point recovery from the initial cardiorespiratory asphyxial compromise may be sufficient to enable survival off ventilator support. Thus a paradoxical outcome may collectively result in which an intervention intended to minimize neurological sequelae may foster the enhanced survival of greater numbers of severely compromised children.

A second effect of cooling is evident in practice. Prior to cooling's introduction, therapeutic efforts in this clinical situation was directed at supportive measures targeting overt symptoms of asphyxial injury (i.e. seizures).[23] Cooling now offers the potential for rescue and improved outcome.[2] Medical culture is intrinsically biased towards action as opposed to inaction. This bias towards action fulfills societal (i.e. parental) expectations to do 'something' to rectify illness and prevent potential adverse outcomes. It may also impart medico- legal expectations. The net result of these biases is to create a therapeutic wedge that is under a continual pressure to expand. Once a therapy, especially one which is relatively benign such as cooling, is available outside the rigid confines of a study protocol with its inclusion and exclusion criteria, there are multiple real life pressures to apply the intervention to those outside of those for whom a definite benefit has been shown through research efforts.

For cooling, this expanded therapeutic wedge may result in practice in the cooling of infants with mild neonatal encephalopathy, for whom there is no need for intervention as all have a relatively benign outcome,[8] and the cooling of infants with a severe neonatal encephalopathy for whom no benefit was demonstrated in the randomized control trials thus far reported.[19,20] Treating children with mild neonatal encephalopathy would result in an overall perception of a greater than real benefit, while treating those with a severe neonatal encephalopathy would result in an overall perception of enhanced worst outcomes, especially when combined with the trend to delay prognostication and a shared decision of withdrawal of care as outlined above. Recognition of these offsetting outcomes may be lost in the statistical noise of the whole spectrum of infants to be cooled or the result may be a 'U-shaped' outcome distribution with a surplus of dichotomous extremes (i.e. normality or severely compromised).

These observations impart the need for clinicians to carefully select those infants to be cooled according to an understanding of the actual results of published studies.[19,20] At the present time, based on the evidence, only infants with a moderate neonatal encephalopathy carefully attributed to objective evidence for intrapartum asphyxia merit cooling.[19,20] Furthermore, we must be aware of the result that cooling may delay prognostication of an adverse outcome, for which the temporal delay in prediction may enable eventual survival. Parents of asphyxiated infants to be cooled must be aware of this possibility and collectively we must be prepared to ensure that such surviving children receive the full gamut of medical, rehabilitation, and support services to which they and their families are entitled.

ACKNOWLEDGEMENTS

Alba Rinaldi provided the necessary secretarial assistance. MCH Foundation for salary support for MS during the writing of this manuscript. MS also benefited from the NeuroDevNet NCE.

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