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Off-Label Use of Therapeutic Hypothermia for Infants with Hypoxic-Ischemic Encephalopathy

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Physicians are often under pressure to use only those therapies that have been shown to be safe and effective in large randomized control trials (RCTs). This is a thorny issue in the newborn intensive care unit: neonatologists recognize the importance of evidence-based decision making [1], but must often rely on treatments that have precedents of clinical use, but little systematic evaluation [1]. Examples of seemingly benign therapies ultimately found to be harmful are reminders of the need for prospective evaluation of new therapies' short- and long-term effects. In the 1940s, neonatologists learned that supplemental oxygen, delivered abundantly to premature babies with respiratory distress syndrome, was toxic to the developing retina and associated with thousands of cases of blindness [2, 3]. More recently we have learned that systemic corticosteroids, seemingly a promising tool for decreasing the impact of bronchopulmonary dysplasia, appear to increase the risk of significant neurodevelopmental impairment [4]. The tension between the need for evidence-based practice and the need to “do something” is well illustrated by exploring the ethical implications of off-label use of therapeutic hypothermia for premature infants with hypoxic ischemic encephalopathy.

Background

Perinatal-neonatal hypoxic ischemic encephalopathy (HIE) is a serious condition caused by acute and unexpected disruption of blood flow and oxygen delivery to the fetus around the time of birth. Infants with HIE may be quite ill with neurologic dysfunction and multisystem organ failure. Roughly 60 percent of infants with HIE die or carry long-term neurologic impairment [5]; in the worst cases, infants are minimally interactive; require intensive support of breathing, circulation, and vital organ function; and are completely and permanently dependent on caregivers.

Until recently, there was no specific treatment for HIE. Supportive care was offered and, in some cases, withdrawn if the neurologic prognosis seemed particularly grim. In other cases physiologic function returned but full neurologic function did not, an outcome some physicians and parents consider to be a “fate worse than death” [6-8].

With improved understanding of the pathophysiology of HIE, we now understand that lowering body temperature attenuates the cellular response to hypoxic-ischemic injury, interrupting the cascade of events that appears to contribute to poor outcomes [9]. A number of large RCTs have shown that reduction of head or whole-body

temperature to 3 degrees below normal for 3 days is associated with a 40 to 50 percent reduction in death and long-term disability in term infants with moderate or severe encephalopathy [5], with side effects that are readily manageable and usually of trivial clinical significance. Initiation of therapeutic hypothermia (TH) within 6 hours of birth has rapidly become the standard of care in many NICUs around the developed world [10-12].

An early concern about TH was that treatment would not reduce the total number of poor outcomes but, rather, redistribute them from death to survival with severe neurologic impairment [13]. Fortunately, meta-analyses have shown that the absolute incidence of neurologic disability does not increase [14, 15].

Although the RCT results are reassuring, there is potential for serious adverse effects and sub-optimal outcomes, and current recommendations advise that TH only be used in a manner consistent with published protocols [16-18]. As researchers explore use of TH for infants who are gestationally younger or chronologically older, along with other “optimized” protocols, available recommendations are to limit these applications to clinical trials [19].

Therapeutic Hypothermia for Preterm Infants

Premature infants (born at 36 gestational weeks or younger) may be vulnerable to HIE, but the incidence in this population is unknown [20, 21], as they have traditionally been excluded from the diagnosis due to overlap between normal neurologic findings in this population and HIE diagnostic criteria [22-24]. Although most of the randomized trials included infants of 36 weeks gestation, experience with TH for premature babies younger than 36 weeks’ gestation is largely anecdotal.

Prevention of hypothermia is a cornerstone of care for premature infants [25, 26], which complicates the use of TH in this patient population. In addition, the complexity of the developing brain (even among “late preterm” infants [27]) obscures our understanding of the impact of HIE, hypothermia, and other pathophysiologic states that accompany preterm birth [28]. One randomized pilot study comparing selective head cooling and supportive therapy for preterm infants began recruitment but was halted by the Food and Drug Administration due to safety concerns after the initial patients were randomized [29, 30]. Presently, the only possible approach to targeted therapy for premature infants with suspected HIE is the off-label use of TH.

Arguments in Favor of Off-Label Use of TH for Premature Infants

Considerations for individual patients. Theoretically, 1- or 2-week distinctions in gestational age are unlikely to result in significantly different outcomes and side effects, particularly as infants approach full term. Many routine neonatal therapies are based on this kind of reasoning, extrapolated from either clinical experience or studies in older children, infants, or even adults [31, 32]. Furthermore, in the absence of alternative therapies, are we not obligated try *something*, given the risk of poor outcomes for patients with HIE? This reasoning may resonate with many

neonatologists who face desperate parents and dire circumstances and seemingly have little to lose. In these situations, biologic plausibility may be the best foundation on which to base treatment decisions, and the acceptability of using an off-label therapy might be supported by proposing that, provided that parents are given the available information about possible risks and benefits and also offered standard (supportive) therapy, it is within their purview to choose off-label TH.

Societal arguments. This kind of boundary testing can play an important role in medical progress. Such arguments have been important in surgery, where the line can be blurred between trying something for the first time and gaining clinical experience with an innovative procedure [33, 34]. Subjecting a new surgical technique to randomization removes the advantage of allowing the skilled surgeon to “tweak” the procedure gradually [34]. Surely every minute change in a surgical approach does not warrant a RCT [35]; rather, the end result of a subtle series of changes can be systematically compared with the original procedure. Similarly, neonatologists could argue that refinement in neonatal procedures and therapy is a continuous process that drives progress in patient care and generates compelling hypotheses that can subsequently be tested.

Finally, neonatologists may find themselves in dire straits if they commit to using only therapies that have been systematically evaluated. Many routine practices, such as standardized cardiopulmonary resuscitation or use of total parenteral nutrition, have never been evaluated by RCT (and probably never will) because doing so would be ethically or logistically unacceptable. Furthermore, while RCT inclusion criteria may have excluded infants with comorbid conditions that affect trial endpoints (e.g., congenital anomalies), it generally does not follow that infants with those conditions should not be treated with therapies found to be effective in those trials—available clinical evidence is only one aspect of good patient care, which should also include individualized risk-benefit considerations [36].

Arguments in Favor of Limiting the Use of TH to Published Inclusion Criteria

Considerations for individual patients. Biologic plausibility may appear to be an adequate basis on which to treat an infant with an unvalidated therapy, but it fails to address the possibility that assumptions about safety and efficacy are incorrect. With so little knowledge of the epidemiology and natural history of HIE in premature infants and the potential for interaction of pathophysiologic injury mechanisms, complex factors that result in preterm birth, and hypothermia, there is no certainty that preterm infants treated with TH will be better off than those who receive supportive care.

An example of this is the possibility that among premature (as opposed to term) infants treated with TH, there *will* be a redistribution of poor outcomes from death to severe disability, rather than an absolute reduction in both. Studies of many neonatal interventions include formal neurodevelopmental evaluation at 18 to 24 months of age, adding at least 2 years from the completion of recruitment for publication of results. Without longitudinal evaluation of that sort, accumulated clinical experience

may shed some light on the short-term effects of providing TH to preterm infants with HIE without ensuring that the treatment is both efficacious and safe in the long run. Unless they are quite large, prospective registries may not adequately elucidate the effect of TH on complex, multifactorial outcomes like neurologic impairment.

From this standpoint, informed consent may be viewed as necessary but not sufficient to justify the use of off-label therapies. Despite their role as accepted surrogate decision makers for children, parents' decision making is constrained by law to choices that are deemed to be in a child's best interest. For example, in most cases parents may not refuse antibiotics for serious infections, surgical intervention for appendicitis, or chemotherapy for acute leukemia. Similarly, parents may not demand antibiotics for viral infections, X-rays that will not aid in diagnosis, or unnecessary surgery. Regardless of parental preferences, physicians retain the authority and responsibility to practice medicine within the confines of appropriate and rational care.

Societal arguments. A randomized trial of TH for preterm infants with HIE is being planned within the Neonatal Research Network (a network of academic newborn intensive care units that conducts multicenter studies funded by the National Institute of Child Health and Human Development). Rapid completion of the trial becomes more difficult if the therapy is being offered "off protocol," both by slowing the recruitment of patients and by potentially disturbing the state of equipoise that is needed for an ethically permissible trial [37].

Delaying the completion of clinical trials may extend the period in which patients are exposed to the possible harms of TH, such as bleeding and hemodynamic instability or even a higher incidence of neurologic morbidity and mortality. An example of this can be found in the breast cancer literature: women sought aggressive, unproven treatment outside of clinical trials, delaying the discovery that these risky bone marrow transplants were harmful, rather than helpful [38].

Even if the trials are completed, the results may be difficult to generalize if eligible patients are not well represented by the group of study participants due to recruitment difficulties. Conversely, if TH is found to be helpful in reducing the incidence of poor outcomes for premature babies with HIE, delay in completion of the trials may prolong the period in which some infants are denied this benefit [37].

Conclusions

Review of the ethical considerations for and against use of off-label TH for preterm infants with HIE does not resolve the question of whether or not this practice is ethically justifiable—there are compelling arguments on both sides. However, the framework used here can be applied to consideration of other off-label therapies in neonatal and pediatric patients; this includes review of available information about potential risks and benefits, careful balancing of parental autonomy and the child's best interest, an appropriate process of informed consent, and consideration of whether there is an opportunity to systematically evaluate the therapy. As new

treatments are introduced to neonatal intensive care, considerations for and against using off-label and unvalidated therapies should be similarly analyzed.

References

1. Brierley J, Larcher V. Lest we forget... research ethics in children: perhaps onerous, yet absolutely necessary. *Arch Dis Child*. 2010;95(11):863-866.
2. Wilson JL, Long SB, Howard PJ. Respiration of premature infants: response to variations of oxygen and to increased carbon dioxide in inspired air. *Arch Pediatr Adolesc Med*. 1942;63(6):1080-1085.
3. Silverman WA. Oxygen therapy and retrolental fibroplasia. *Am J Public Health Nations Health*. 1968;58(11):2009-2011.
4. Barrington KJ. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. *BMC Pediatrics*. 2001;1:1.
5. Higgins RD, Shankaran S. Hypothermia: novel approaches for premature infants. *Early Hum Dev*. 2011;87 Suppl 1:S17-S18.
6. van der Worp HB, Greving JP. Surviving space-occupying cerebral infarction: a fate worse than death? *Neurology*. 2010;75(8):676-677.
7. Livingston DH, Tripp T, Biggs C, Lavery RF. A fate worse than death? Long-term outcome of trauma patients admitted to the surgical intensive care unit. *J Trauma*. 2009;67(2):341-348.
8. Fry J LJ, Andrews B, Meadow M. Is there a fate worse than death? And if so, what is its epidemiology [abstract 2120.4]? Pediatric Academic Societies' Annual Meeting; Baltimore MD; May 2-5, 2009.
9. Pfister RH, Soll RF. Hypothermia for the treatment of infants with hypoxic-ischemic encephalopathy. *J Perinatol*. 2010;30 Suppl:S82-S87.
10. Roehr CC, Hansmann G, Hoehn T, Buhner C. The 2010 Guidelines on Neonatal Resuscitation (AHA, ERC, ILCOR): similarities and differences - what progress has been made since 2005? *Klin Padiatr*. 2011;223(5):299-307.
11. Landau Y, Berger I, Marom R, et al. Therapeutic hypothermia for asphyxiated newborns: experience of an Israeli tertiary center. *Isr Med Assoc J*. 2011;13(1):29-33.
12. Biban P, Filipovic-Grcic B, Biarent D, Manzoni P. New cardiopulmonary resuscitation guidelines 2010: managing the newly born in delivery room. *Early Hum Dev*. 2011;87 Suppl 1:S9-S11.
13. Perlman M, Shah P. Ethics of therapeutic hypothermia. *Arch Paediatr*. 2009;98(2):211-213.
14. Tagin MA, Woolcott CG, Vincer MJ, Whyte RK, Stinson DA. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis. *Arch Pediatr Adolesc Med*. 2012;166(6):558-566.
15. Shah PS. Hypothermia: a systematic review and meta-analysis of clinical trials. *Semin Fetal Neonatal Med*. 2010;15(5):238-246.

16. Hoehn T, Hansmann G, Buhner C, et al. Therapeutic hypothermia in neonates. Review of current clinical data, ILCOR recommendations and suggestions for implementation in neonatal intensive care units. *Resuscitation*. 2008;78(1):7-12.
17. Wachtel EV, Hendricks-Munoz KD. Current management of the infant who presents with neonatal encephalopathy. *Curr Probl Pediatr Adolesc Health Care*. 2011;41(5):132-153.
18. Kattwinkel J, Perlman JM, Aziz K, et al. Neonatal Resuscitation: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Pediatrics*. 2010;126(5):e1400-e1413.
19. Christensen RD, Sheffield MJ, Lambert DK, Baer VL. Effect of therapeutic hypothermia in neonates with hypoxic-ischemic encephalopathy on platelet function. *Neonatology*. 2012;101(2):91-94.
20. Schmidt J, Walsh WF. Hypoxic-ischemic encephalopathy in preterm infants. *J Neonatal-Perinatal Med*. 2010;3(4):277-284.
<http://iospress.metapress.com/content/1854t231m72w111h/>. Accessed September 7, 2012.
21. Salhab WA, Perlman JM. Severe fetal acidemia and subsequent neonatal encephalopathy in the larger premature infant. *Pediatric Neurol*. 2005;32(1):25-29.
22. Volpe JJ. *Neurology of the Newborn*. 5th ed. Philadelphia: Saunders/Elsevier; 2008.
23. Fenichel GM. *Neonatal Neurology*. 4th ed. Philadelphia: Churchill Livingstone Elsevier; 2007.
24. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol*. 1976;33(10):696-705.
25. Silverman WA, Fertig JW, Berger AP. The influence of the thermal environment upon the survival of newly born premature infants. *Pediatrics*. 1958;22(5):876-886.
26. Jolly H, Molyneux P, Newell DJ. A controlled study of the effect of temperature on premature babies. *J Pediatr*. 1962;60:889-894.
27. Woythaler MA, McCormick MC, Smith VC. Late preterm infants have worse 24-month neurodevelopmental outcomes than term infants. *Pediatrics*. 2011;127(3):e622-e629.
28. Gunn AJ, Bennet L. Brain cooling for preterm infants. *Clin Perinatol*. 2008;35(4):735-748, vi.
29. Walsh WF, Hobson A, Reese C. Survival of infants between 32-35 weeks gestation treated with hypothermia for hypoxic ischemic encephalopathy (HIE) [abstract 3675.4]. Pediatric Academic Societies' Annual Meeting; Vancouver, CA; May 1-4, 2010.
30. US National Institutes of Health. Pilot study of head cooling in preterm infants with hypoxic ischemic encephalopathy. <http://clinicaltrials.gov/ct2/show/NCT00620711?term=cooling+and+pre+premature&rank=1>. Accessed September 7, 2012.

31. Roberts R, Rodriguez W, Murphy D, Crescenzi T. Pediatric drug labeling. *JAMA*. 2003;290(7):905-911.
32. Amin SB, McDermott MP, Shamoo AE. Clinical trials of drugs used off-label in neonates: ethical issues and alternative study designs. *Account Res*. 2008;15(3):168-187.
33. Reitsma A, Moreno JD. Ethics of innovative surgery: US surgeons' definitions, knowledge, and attitudes. *J Am Coll Surg*. 2005;200(1):103-110.
34. Burger I, Sugarman J, Goodman SN. Ethical issues in evidence-based surgery. *Surg Clin N Am*. 2006;86(1):151.
35. McKneally MF. Ethical problems in surgery: innovation leading to unforeseen complications. *World J Surg*. 1999;23(8):786-788.
36. Guyatt GH, Rennie D. *Users' Guides to the Medical Literature: A Manual For Evidence-Based Clinical Practice*. Chicago, IL: American Medical Association; 2002.
37. Clark WF, Garg AX, Blake PG, Rock GA, Heidenheim AP, Sackett DL. Effect of awareness of a randomized controlled trial on use of experimental therapy. *JAMA*. 2003;290(10):1351-1355.
38. Vogl DT, Stadtmayer EA. High-dose chemotherapy and autologous hematopoietic stem cell transplantation for metastatic breast cancer: a therapy whose time has passed. *Bone Marrow Transplant*. 2000;37(11):985-987.

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