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Ethical issues in neonatal research involving human subjects

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ABSTRACT

Research involving critically ill neonates creates many ethical challenges. Neonatal clinical research has always been hard to perform, is very expensive, and may generate some unique ethical concerns. This article describes some examples of historical and modern controversies in neonatal research, discusses the justification for research involving such vulnerable and fragile patients, clarifies current federal regulations that govern research involving neonates, and suggests ways that clinical investigators can develop and implement ethically grounded human subjects research.

Clinical research involving patients in neonatal intensive care units (NICUs) over the past 60 years has resulted in extraordinary advances in neonatal care and has decreased morbidity and mortality for countless newborns. Those who practice in NICUs know that the sickest patients in academic medical centers are frequently also the smallest. These infants suffer from the serious consequences of preterm birth, congenital abnormalities, chronic and acute infections, and perinatal asphyxia. So it should be no surprise that clinicians caring for sick neonates seek to do research to enhance the care and outcomes of their patients. Yet, historically, neonatal care and neonatal research has been fraught with many controversies. Neonatal clinical research has always been hard to perform, is very expensive, and has always generated unique ethical concerns. In this article, I will attempt to describe some examples of historical and modern controversies in neonatal research, discuss the justification for research that involves such vulnerable and fragile patients, clarify current federal regulations that govern research involving neonates, and suggest ways that clinical investigators can develop and implement ethically grounded research protocols involving neonates.

Historical and modern controversies in neonatal research

There have been many clinical misadventures in neonatal care directly related to the lack of research to provide evidence of efficacy and lack of toxicity of universally used early intensive care practices. Rapid infusion of concentrated bicarbonate for the correction of metabolic acidosis, chloramphenicol for neonatal sepsis, use of oxygen for apnea of prematurity, use of high pressures for ventilating full-term infants with severe hypoxia, to name a few, all resulted in increased mortality and morbidity for critically ill neonates. Why were neonatologists using such dangerous practices? Were these well-intentioned, caring physicians suffering from a "therapeutic imperative," the need to provide some level of treatment for a critically ill patient,

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often a treatment that had been used by others over many years, even if that therapy had never been shown to be safe and effective?[1] As the field of neonatology developed in the 1960s and 1970s with the development of subspecialty certification and the creation of academic fellowship programs, clinicians began to question many NICU practices and to embark on more sophisticated clinical trials. But it was not until 1986 when the National Institute of Child Health and Human Development (NICHD) created the Neonatal Research Network to fund multicenter clinical research in NICUs that large trials were possible.

The history of two common neonatal therapies, extracorporeal membrane oxygenation (ECMO), and the use of oxygen for apnea of prematurity can provide some understanding of the critical importance of research in determining practice, and raise some questions about neonatal research that will need to be answered.

ECMO

The successful use of short-term cardiopulmonary bypass for adults during open heart surgery in the 1950s caused innovative pediatric clinicians in the 1960s to try long-term bypass for preterm neonates with severe respiratory distress syndrome. This innovative therapy resulted in the death of these premature infants from hemorrhage due to the need for anticoagulation, but showed that the technology could be adapted to such small patients. In the 1970s, ECMO began to be used extensively for full-term infants with respiratory failure and pulmonary hypertension refractory to the current therapy and likely to die based on historical experience. Many reports of successful case series motivated large academic medical centers to develop ECMO programs and to recommend its use for term neonates with intractable respiratory failure. While ECMO programs were being developed in an increasing number of NICUs in the 1980s, two important observations were being made. First, many ECMO survivors were found to have significant brain damage and profound neurodevelopmental delay. Second, new medical approaches to treat respiratory failure and pulmonary hypertension were shown to be very successful for infants who were previously thought to be candidates for ECMO, and these infants seemed to have fewer injuries in their brains, although they still had significant neurodevelopmental delay. Randomized, controlled studies of ECMO were difficult to perform. ECMO technology and medical therapies for neonatal respiratory failure were changing rapidly, the number of patients so sick as to require these treatments was not very large, and the risks of the surgical vs. the medical approaches were quite different.[2] Yet, multi-center, randomized, clinical trials could have been initiated in the 1970s to answer many of the questions about the safety and efficacy of this innovative therapy. This example raises some interesting questions. Can we justify research involving such fragile and vulnerable subjects? Is it ethical to withhold innovative therapies that might benefit critically ill neonates by creating a randomized trial?

Oxygen and retrolental fibroplasia—Retinopathy of prematurity (ROP)

After 60 years of neonatal intensive care, we still do not know the optimal level of oxygen that should be administered to critically ill preterm neonates. In the 1950s, it was recognized that vasculoproliferative changes in the retina of surviving preterm infants were associated with unrestricted use of oxygen to prevent apnea. Early randomized clinical trials of restricted vs. unrestricted use of oxygen showed that restricted use of oxygen significantly decreased the severity of ROP and the number of premature infants who became blind. The institution of restricted oxygen use into general neonatal practice was associated with a dramatic reduction in ROP and a concomitant increase in death and cerebral palsy.[3] In the 1970s and 1980s, the ability to continually measure oxygenation status in neonates became possible. Transcutaneous oxygen monitoring, and then, measurement of oxygen saturation (SpO_2) of hemoglobin by pulse oximetry was developed. By the early 2000s, continuous pulse oximetry measurement was used for all sick preterm infants and recommended levels of SpO_2 ranged from 85% to 95%. Thus, it became possible to ask the question: can maintaining SpO_2 in the lower half of the accepted range for very low birth weight preterm infants decrease the incidence of severe ROP without increasing death and other significant adverse outcomes?

This resulted in the SUPPORT (Surfactant Positive Pressure and Oxygenation Randomized Trial) Trial.[4] This research study sponsored by the NICHD Neonatal Research Network was a stratified trial involving preterm infants from 24 weeks 0 days to 27 weeks 6 days gestation randomized into two groups to compare outcomes at SpO_2 of 85–89% vs 91–95%. The study recruited 1316 infants in 2004–2009 at 23 major U.S. neonatal programs. The study found that the rate of the composite primary outcome, severe retinopathy or death, did not differ significantly between the lower oxygen saturation group and the higher oxygen saturation group, but the rate of severe ROP was lower in the lower oxygen group, and the rate of death before discharge was lower in the higher oxygen group. These surprising results were confirmed by several other international studies and have affected how oxygen is administered in NICUs across the world.

An interesting controversy occurred after the results of the SUPPORT study were published in 2010.[4] The Office for Human Research Protections of the Department of Health and Human Services (DHHS) criticized the NICHD and each of the academic medical centers that had participated in the trial for providing an informed consent that did not adequately describe the reasonably foreseeable risk of death, and that the investigators and the Institutional Review Boards (IRBs) incorrectly believed that because all infants were randomized within the standard range for SpO_2, that the study involved no more than minimal risk. This controversy raised some fundamental questions. How can we justify placing neonates at significant risk in a research trial? While critically ill patients in NICUs are often at serious risk of death and future disability, how much incremental risk were the participants exposed to by the study itself? Did the study involve only minimal risk? Was there sufficient information shared with parents who were asked to consent for their infants to enter the trial?

This neonatal controversy is part of a larger critique that holds that the current U.S. regulatory framework for governing protection of human research participants is an