Seminars in Fetal & Neonatal Medicine 20 (2015) 431–435

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Review

The ethics of neonatal research: A trialists' perspective

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Keywords:
Ethics
Research
Infant
Newborn
Randomized controlled trial

SUMMARY

We are neonatal physicians who strive to practice evidence-based medicine. We conduct and promote randomized trials in preterm and critically ill infants to improve their care and outcomes. Controlled clinical trials are ethical and essential because randomization is the best strategy to minimize bias when evaluating therapies of uncertain benefit. Perinatal and neonatal randomized trials have identified better care practices, uncovered useless or harmful therapies, and revealed new knowledge gaps. We are convinced that neonatal randomized trials can be done safely and in partnership with the infants' families.

1. Introduction

> "We cannot always make our patients better, but we can always make them worse."
>
> William A. Silverman. *Where's the evidence? Debates in modern medicine* (Oxford University Press, 1999)

We are neonatal physicians who strive to practice evidence-based neonatal medicine [1].We conduct randomized clinical trials to add to the body of evidence that informs our treatment decisions. Because randomization is the best strategy to minimize bias and erroneous conclusions about treatment effects, we believe that neonatal practitioners have an ethical and moral obligation to perform controlled trials of widely used neonatal therapies.

Is a baby who participates in a controlled trial a "guinea-pig"? The correct answer is "it depends". It depends on the quality of the research question, the design and implementation of the trial, and on the integrity of the consent process. Importantly, however, many babies become "guinea-pigs" in our daily clinical practice. Every time we prescribe an unproven therapy, our patients participate – often without explicit parental consent – in an uncontrolled experiment that may unwittingly put them at risk but contributes little if any meaningful new knowledge.

Two brief scenarios illustrate that clinical trials are safe and improve the care of babies.

1. The neonatal team is called to the delivery of an extremely preterm infant. Her mother was admitted to the hospital two days prior with severe pre-eclampsia. Antenatal corticosteroids were prescribed because of threatened preterm birth. The mother's condition remains unstable, prompting the obstetrician to deliver the baby. Wrapped in plastic under a radiant warmer, the baby takes a few gasping breaths and immediately receives continuous positive airway pressure (CPAP).
2. The neonatal team re-convenes in the delivery room to receive a full-term baby who is born through meconium-stained amniotic fluid after his mother was induced at 41 weeks of gestation. The infant is vigorous and breathing regularly but with labored respirations. CPAP is initiated with room air. A pulse oximetry probe is placed on the baby's right wrist and the concentration of supplemental oxygen is slowly increased to 40% to achieve oxygen saturations in the desired target range.

2. Perspective I: Neonatal randomized trials identify better care practices

Randomized clinical trials and meta-analyses of those trials informed the care of both infants (Boxes 1 and 2). In the case of the preterm infant, antenatal corticosteroids administered to women with threatened preterm birth have been shown conclusively to reduce the risks of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and mortality [2].

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http://dx.doi.org/10.1016/j.siny.2015.08.004
1744-165X/

Box 1
Examples of evidence-based care of the very preterm infant.

What is known: DO

- Use antenatal corticosteroids for women with threatened preterm birth to reduce the risks of respiratory distress syndrome, IVH, necrotizing enterocolitis and mortality [2].
- Use noninvasive respiratory support in the delivery room whenever possible to reduce the risk of death or BPD [3].
- Use early selective surfactant to treat established respiratory distress syndrome in infants requiring assisted ventilation to reduce the risks of death and BPD [4].
- Use caffeine to reduce the risks of BPD and death or NDI and to improve motor function in childhood [5–7].

What is known: DON'T

- Use early postnatal corticosteroids (<8 days) to reduce the risk of BPD because of increased risks of gastrointestinal perforation and cerebral palsy [8].
- Use inhaled nitric oxide to reduce the risks of death, BPD, or NDI [9].
- Use routine opioid analgesia in ventilated preterm infants to reduce the risk of death or severe brain injury [10].
- Use glutamine supplementation to reduce the risks of mortality, invasive infection, necrotizing enterocolitis, or NDI [11].

What is unknown?

- Does delayed cord clamping or cord milking improve survival or developmental outcomes? [12]
- Does liberal use of red blood cell transfusions improve survival without NDI? [13,14]
- Does inositol reduce the risk of death, retinopathy of prematurity, or IVH? [15]
- Does nutrient-fortified donor human milk improve survival and developmental outcomes for infants whose mothers' own milk is unavailable? [16]

IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; NDI, neurodevelopmental impairment.

Box 2
Examples of evidence-based care of the full-term infant.

What is known: DO

- Begin resuscitation in the delivery room with room air and titrate supplemental oxygen to achieve saturations similar to those of healthy full-term infants to reduce the risk of death [17].
- Begin therapeutic hypothermia within 6 h after birth for infants with moderate or severe encephalopathy, using criteria and a protocol similar to published trials, to reduce the risks of death and NDI [18].
- Use inhaled nitric oxide for persistent pulmonary hypertension of the newborn to reduce the risk of death or need for ECMO [19].
- Feed mother's own milk whenever possible to reduce the risks of gastrointestinal tract infection and atopic eczema and improve cognitive outcomes [20,21].

What is known: DON'T

- Delay delivery beyond 41 completed weeks of gestation because of increased risk of perinatal death, meconium aspiration syndrome, and caesarean section [22].
- Routinely suction the oropharynx or nasopharynx before delivery of the shoulders and body or suction the trachea of the vigorous baby born through meconium stained fluid [23–25].
- Perform therapeutic hypothermia for longer or at lower temperatures than standard because this does not reduce mortality in infants with moderate to severe encephalopathy [26].
- Restrict pacifier use until after lactation is established to increase duration of breastfeeding [27].

What is unknown?

- Should we routinely perform endotracheal suctioning of the non-vigorous baby born through meconium stained fluid? [25]
- Does delayed cord clamping reduce the risk of death or improve developmental outcomes? [28]
- What adjunctive therapies in addition to cooling improve outcomes of infants with encephalopathy? [29]
- Does naloxone reduce risk of intensive care admission or improve breast feeding in infants exposed in utero to opiates? [30]

NDI, neurodevelopmental impairment; ECMO, extracorporeal membrane oxygenation.

In the delivery room, the infant is stabilized with CPAP rather than endotracheal intubation with administration of prophylactic surfactant, as would have been done routinely in many hospitals just few years ago. Recent randomized trials compared both approaches and demonstrated that very preterm infants with respiratory distress syndrome can safely be supported non-invasively [31–33]. A meta-analysis of these trials confirmed that an attempt to avoid endotracheal intubation is associated with lower rates of death or bronchopulmonary dysplasia (BPD) at 36 weeks of postmenstrual age and with no increase in adverse events [3].

The labored respirations of the term infant in our second scenario are initially supported with CPAP and room or ambient air. This is a change from prior practice in the developed world where most newborns were resuscitated after birth with pure oxygen. Methodical experimental research led to the hypothesis that pure oxygen may be toxic and this hypothesis was tested in a series of controlled trials. Collectively they showed that beginning the resuscitation with ambient air reduces mortality [17]. It has been estimated that “more than 100 000 newborn lives could be saved globally each year by switching from pure oxygen to ambient air for newborn resuscitation” [34].

In both cases, controlled clinical trials identified care practices that were better than the prevailing “routine” practices.

Additional examples of evidence-based therapies for both the extremely preterm and the full-term infant are listed in Boxes 1 and 2. These therapies include caffeine for periodic breathing and apnea of prematurity to reduce the risks of BPD, neurodevelopmental