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Neonatal research ethics after SUPPORT

John D. Lantos*

Children's Mercy Hospital, Kansas City, MO, USA

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A B S T R A C T

The SUPPORT study (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments), sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development to evaluate different oxygen saturation targets for extremely premature babies, led to a national controversy that was surprisingly public, intense, and polarizing. This article describes the study design, the study outcomes, and the key issues. I conclude that the controversy was based on two different views of the clinical investigator. One, held by investigators themselves, is that investigators are primarily committed to the patient's well-being. The other sees the investigator as unable to disentangle his conflicting loyalties and as inevitably prioritizing the goals of research over the goals of patient care. I suggest that our current oversight systems overstate the risks of research and understate the risks of idiosyncratic practice variation. A better system would treat the relative risks of these two phenomena as comparable.

1. Introduction

The controversy over the SUPPORT study (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) of oxygen saturation targets in extremely premature babies was surprisingly public, intense, and polarizing. In order to understand the controversy and its implications, I first describe the study design and the study outcomes, then review the issues that led to controversy, and finally discuss the implications.

2. SUPPORT study design

Between 2005 and 2009, infants born between 24 and 27 weeks of gestation were randomized to two different oxygen saturation targets. One group was randomly assigned to a target range of oxygen saturation of 85–89% (the lower-oxygen-saturation group). The other group was randomized to 91–95% (the higher-oxygen-saturation group).

This targeting of oxygen saturation was initiated within the first 2 h after birth and was continued until 36 weeks of postmenstrual age or until the infant was breathing ambient air and did not require ventilator support or continuous positive airways pressure for >72 h. The target ranges were kept unchanged from birth until 36 weeks of postmenstrual age.

Blinding was maintained with the use of electronically altered pulse oximeters. For babies in the low-oxygen group, an oximeter reading of 90% corresponded to actual levels of oxygen saturation of 87%. For babies in the high-oxygen group, that same reading corresponded to an actual saturation of 93%. The oxygen-saturation reading gradually changed and reverted to actual values when it was <84% or >96% in both treatment groups. Doctors, nurses, and respiratory therapists were then asked to maintain oxygen saturations between 88% and 92% in all babies, knowing that, by doing so, some would have oxygen saturations of 85–89% and others would have saturations of 91–95%.

The primary outcome of the study was a combined variable of severe retinopathy or death. All surviving infants were followed by ophthalmologists. Eyes were examined beginning at 33 weeks of postmenstrual age and continued until the study outcome was reached or resolution occurred. Retinopathy was treated using standard protocols which could have included laser therapy, cryotherapy, both laser therapy and cryotherapy, scleral buckling, or vitrectomy.

An independent data and safety monitoring committee reviewed results at approximately 25%, 50%, and 75% of planned enrollment.

The study was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. It was approved by the institutional review board at each participating site. Written informed consent was obtained from the parent or guardian of each

* Children's Mercy Hospital, 2401 Gillham Road, Kansas City, MO 64108, USA.
E-mail address: jlantos@cmh.edu.

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child before delivery.

3. Study results

The study results were published in two papers in the *New England Journal of Medicine* (*NEJM*) [1]. The first paper, in 2010, reported short-term outcomes. There was no difference in the rate of the combined outcome of "severe retinopathy or death before discharge" between the lower- and higher-oxygen-saturation groups (28.3% and 32.1%, respectively). There was, however, a statistically significant difference in death before discharge. This occurred in 130/654 (19.9%) of infants in the lower-oxygen-saturation group compared with 107/662 (16.2%) of infants in the higher-oxygen-saturation group (relative risk (RR) with lower oxygen saturation: 1.27; 95% confidence interval (CI): 1.01–1.60; $P = 0.04$).

The rate of severe retinopathy among survivors was lower in the lower-oxygen-saturation group (8.6% vs 17.9%; RR: 0.52; 95% CI: 0.37–0.73; $P < 0.001$). Babies in the lower-oxygen-saturation group were less likely to require supplemental oxygen at 36 weeks post-conceptual age.

In a follow-up paper in 2012 [2], researchers reported that there were no statistically significant differences in the rates of neurodevelopmental impairment at 18–22 months between the groups (30.2% vs 27.5%; RR: 1.12; 95% CI: 0.94–1.32; $P = 0.21$).

4. The controversy

The controversy began on March 7th, 2013, when the federal Office for Human Research Protections (OHRP) notified University of Alabama at Birmingham (UAB) that it had concerns about the informed consent forms in the study [3]. They found fault with the consent form for not including information about "prior research and analyses that had been done looking at the relationship between oxygen and ROP [retinopathy of prematurity]" and not identifying "any specific risk relating to randomizing infants to a high or low range of oxygen." This, OHRP claimed, was in violation of federal regulations that require all informed consent forms for research to include "a description of any reasonably foreseeable risks and discomforts." OHRP requested that UAB provide OHRP with a plan to improve the ways in which they would "adequately address the basic elements of consent as required by HHS [Health and Human Services] regulations."

A month later, a Washington-based lobbying group, Public Citizen, wrote to the Secretary of Health and Human Services alleging that OHRP had not gone far enough [4]. Public Citizen claimed that "any study comparing the two experimental target levels of oxygen saturation would be both unethical and not compliant with requirements of HHS regulations." They demanded that HHS issue "a formal apology to the parents of all 1316 infants who participated in the SUPPORT study."

A few days later, on April 15th, an editorial in the *New York Times* asserted that the SUPPORT study "failed to meet the most basic standard: providing an informed consent document to parents that accurately described the risks and benefits of the research to be conducted." [5].

Two days later, an editorial in the *NEJM* defended the study, the consent form, and the investigators. Editor-in-Chief Drazen wrote that the consent document for the SUPPORT study "… addressed the prevalent knowledge fairly and reasonably." He claimed that, at the time that the study was designed, "there was no evidence to suggest an increased risk of death with oxygen levels in the lower end of a range viewed by experts as acceptable, and thus there was not a failure on the part of investigators to obtain appropriately informed consent from parents of participating infants." Drazen concluded that the investigators were being faulted with not knowing (and therefore disclosing) a risk that was not known until the study showed it to be present. "This is how new medical knowledge is gained," he concluded.

In the same issue of the *NEJM,* two prominent bioethicists defended the study and argued that OHRP's actions were wrong. They wrote, "The OHRP is asking that research be described as riskier than it really is and is suggesting that the parents were duped into enrolling their frail infants in dangerous research. Not only is that not true, but it also poses substantial risk to the conduct of valuable comparative effectiveness research both for premature infants and for the general public who continue to face too many treatments where uncertainty prevails about what is best." [6].

The bioethics community was divided in their response to the controversy. One group of ethicists argued that, "The infants included in the study were randomly assigned to oxygen-saturation targets that were consistent with standard clinical care at the participating institutions. The conclusion of the OHRP that the study's experimental evaluation of these otherwise routinely used oxygen-saturation levels exposed subjects to additional risk (above the risks of routine clinical treatment) is not supported by the evidence." [7] Another group came to the opposite conclusion [8]. They wrote, "The potential risks and benefits of being in the study could not be said to be the same as the potential risks and benefits of receiving care outside the study." They concluded that the consent forms were deficient and thus that OHRP's actions were appropriate. Neither group addressed Public Citizen's more wide-ranging critiques of the study itself.

Leaders of the National Institutes of Health (NIH) defended the study and the consent process. They wrote, "The investigators (in SUPPORT) had no reason to foresee that infants in one study group would have a higher risk of death than would those in the other group. The babies included in SUPPORT were, of course, facing substantial risks because of prematurity – the same risks as premature babies who were not enrolled in the study – but their care was never compromised for the sake of the study." [9].

At that point, OHRP withdrew its finding that the consent process for SUPPORT was flawed. They acknowledged "widespread misunderstanding of the risks that are required to be disclosed in obtaining informed consent for certain types of clinical trials." [10] In order to help resolve those misunderstandings, OHRP called for an open meeting at the Department of Health and Human Services. At that meeting, 28 speakers offered comments to a panel of leaders from NIH, OHRP, and Food and Drug Administration [11,12].

A year after this meeting, OHRP issued a new "Draft Guidance on disclosing reasonably foreseeable risks in research evaluating standards of care" and asked for public comments [13]. The public was divided [14]. To date, OHRP has not issued a final version of those guidelines, though some of the concerns were addressed in recently issued revisions to the Common Rule [15].

4.1. Legal controversy

In the meantime, a lawsuit was filed on behalf of three children who had been enrolled in the SUPPORT study. The plaintiffs alleged that, "As a result of the careless, negligent, and reckless conduct of the defendants, the plaintiffs and the class were caused to suffer excruciating and agonizing pain, physical discomfort and emotional distress." [16].

The lawsuit was eventually dismissed by a summary judgment [17]. The standards for granting summary judgment in a case like this are very high. The judge, Karon Bowdrie, was required by law to view all of the facts "in the light most favorable to (the plaintiff)," and then decide whether "… reasonable minds could differ on the inferences arising from undisputed facts." [18] If so, then the court

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