Should an IRB Approve a Placebo-Controlled Randomized Trial of Analgesia for Procedural Pain in Neonates?

One of the most controversial issues in neonatology today is the appropriate treatment of procedural pain in the NICU. Infants in the NICU undergo numerous painful procedures. Policies and practices for the treatment of pain vary from NICU to NICU and from doctor to doctor. Numerous studies have been done to clarify the best methods of relieving pain, but the studies themselves are ethically problematic. What is the gold standard? How should we assess pain? When have we learned enough to consider certain practices as proven? Should proven practices be considered as the standard of care, even if we know that they are not widely used? In this ethics column, we asked experts in pain and palliative care to consider a proposed randomized trial for procedural pain in newborns and to discuss whether an institutional review board should approve the trial. Dr Bellieni is a neonatologist and bioethicist in Sienna, Italy. Dr Taddio is a pharmacologist at the Hospital for Sick Children in Toronto. Dr Linebarger is Medical Director of the Palliative Care Program at Children's Mercy Hospital in Kansas City.

THE CASE

The following proposal was submitted to an institutional review board (IRB) at a children's hospital to study different interventions for procedural pain in newborns.

Efficacy of Sucrose and Breast Milk as Analgesia for Procedural Pain in Newborns

Background

Numerous studies reveal that both oral sucrose and breast milk can reduce duration of crying in newborns after a heel stick.¹ Repeated doses of sucrose during prolonged hospital stays are associated with developmental problems. To better understand the efficacy of breast milk and sucrose, we want to test them against placebo. We will recruit 150 healthy full-term newborns. They will be randomly assigned into 3 groups of 50 infants:

"Mother's milk group": each newborn will be given 2 mL mother's milk 2 minutes before the procedure by using a syringe with the needle removed. The milk will be delivered onto the tongue of the newborns, avoiding contact of the syringe with the lips.

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KEY WORDS

pain, placebo, research ethics, randomized trial

ABBREVIATIONS

IRB—institutional review board

PIPP—premature infant pain profile

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“Sucrose group”: each newborn will be given 2 mL of a 20% sucrose solution by using the same procedure described for the mother’s milk group.

“Control group”: each newborn will be given 2 mL of distilled water, using the same procedure.

Outcomes

Each infant will be evaluated during and after the procedure by using the premature infant pain profile (PIPP) and salivary cortisol levels. The PIPP is a multidimensional measure of pain that includes behavioral (brow bulge, eye squeeze, and nasolabial furrow), physiologic (heart rate and oxygen saturation), and contextual (behavioral state and gestational age) indicators. Salivary cortisol, a marker for stress, will be measured by using standard techniques. We will compare the mean PIPP values and salivary cortisol levels of the 3 groups.

The IRB members disagreed about the acceptability of this protocol. Some suggested that sucrose has been clearly established as safe and effective. Thus, they said, it would be unethical to randomly assign infants to placebo and deny them access to a proven analgesic. Others pointed out that sucrose and breast milk were not currently the clinical standard of care for analgesia in most nurseries. They felt that this study would add to a growing body of literature on the efficacy of different forms of analgesia in neonates.

We asked experts to comment on whether placebo-controlled studies for procedural pain in full-term neonates are ethically permissible today.

Carlo V. Bellieni Writes

In this trial, 3 groups of infants undergo painful stimulations. The researchers propose to randomly assign them to 3 different treatments: a standard and well-proven intervention, 1 that may possibly be beneficial, and no

analgesia. The question that this study raises is as follows: Can we choose to expose infants to pain without analgesia during a clinical trial? My answer is “no.”

My opposition is based on the fact that deliberately exposing infants to avoidable pain contrasts with basic ethical rules, the first being the nonmaleficence principle.

One of the main rules of a clinical trial is nonmaleficence: the patient should not be hurt. But, in this trial, we provoke pain, and subjects in the placebo arm are not given any analgesia. We obviously are harming them. Therefore, this trial has a central flaw that makes it unacceptable. Some can argue that because neonatal analgesia is not yet commonly practiced, we can omit it in clinical trials.² But 1 malpractice is not a sufficient reason for another malpractice. Provoking avoidable pain to an infant is inexcusable, because now we have good and safe analgesic treatments. One can say that pain provoked in this study to the control group is minimal and commonly accepted by lay people. But newborns have scarce capacity to endogenously antagonize pain. Therefore, pain due to heel prick is very high, according to all the available neonatal studies. Moreover, even if pain were minimal, we cannot infer that the infant would accept it only “because I would accept it” or because “it is commonly accepted.”

This study also violates the principle of beneficence. According to the Declaration of Helsinki, “in any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic methods.”³ By this principle, the physician is obligated to serve the best interests of each specific patient. In this study, patients in the control group do not receive necessary analgesia.

We have now dealt with trials in which the control group does not receive analgesia. But the same criterion

should be used for trials in which the control group, instead of being given validated analgesia, undergoes maneuvers of nonproven analgesic effect. Rocking, holding the infant, the mother’s voice, and other treatments can soothe the infant, but these maneuvers have not been proven to be as effective as oral sucrose or as topical analgesic creams; therefore, they cannot be used in the control group because new treatments should only be studied against the current gold standard of treatment.

Innovation is, of course, desirable. It is the only way to improve on the current state of the art. But innovation must take place under strict moral rules. The theoretical or clinical bases of the innovation’s effectiveness must be provided by, for example, demonstration of its effectiveness in animal models, or of provoking an increase in blood β -endorphins when administered to humans. This safeguards the infants’ right to wellbeing and protects them from “adventurous” attempts.

In conclusion, this trial is to be rejected because it exposes infants to avoidable pain, a behavior that is anachronistic for modern medicine.

Anna Taddio Writes

There is considerable debate regarding the ethics of using placebos in controlled trials for procedural pain in full-term neonates. Arguments for and against the use of placebos should consider the following: (1) the presence of clinical equipoise regarding existing treatments; (2) the ability of these treatments in a particular study design to provide meaningful scientific data; and (3) the condition being studied and the level of additional risk imposed to patients treated with placebo.

Clinical equipoise is regarded as the starting point for clinical trials. It refers to uncertainty on the part of the relevant expert community (such as

clinicians, parents, or researchers) about what therapy is most effective for a given condition. A clinical trial may be ethical if there is uncertainty over the relative benefits and harms of the pain-relieving regimens being employed. Clinical trials should not be conducted unnecessarily on questions that have already been definitively answered.

Before I could decide whether the proposed study should be approved, I would need answers to some additional questions by the investigators. First, what, exactly, do they hope to add to the existing literature on the treatment of procedural pain in newborns? As written, the protocol does not review previous comparisons of breast milk to sucrose. There are, however, many studies that have addressed this question. Thus, my question to these investigators would be about what, exactly, they hope to add to that existing literature.

When effective treatments are already available, as is the case for the proposed study, placebo-controlled trials may be permissible if they address an important unresolved issue. Researchers should provide a justification for the choice of a placebo control group, as opposed to the other possible control groups. Why are only breast milk and sucrose included in the proposed trial and not nonnutritive sucking on a pacifier? I can imagine valid reasons. Perhaps there is substantial doubt within the relevant expert community regarding the net therapeutic benefit of available therapies due to limitations in previous studies (such as threats to internal or external validity). Perhaps the investigators think that the outcome measures for the proposed study (ie, PIPP, salivary cortisol) differ enough from the outcome used in previous studies (ie, crying) so as to make the current study design more rigorous and reliable. Perhaps

the investigators are looking for an alternative marker of therapeutic effectiveness. Researchers must also specify the clinical standard of care: Does it include the interventions under evaluation (so that participation would potentially result in withholding pain management) or other types of pain-relieving interventions?

Placebos are generally unethical if they are associated with additional risk of severe or irreversible harm. This is not the case in the proposed study. Furthermore, in the current study, the condition being examined (ie, heel lancing) is (presumably) being undertaken as part of regular clinical care. The procedures included in the study (ie, physiologic monitoring, salivary cortisol collection) may be considered only a minor increase above minimal risk (research in which the probability and magnitude of possible harms implied by participation in the research is no greater than those encountered by participants in those aspects of their everyday life that relate to the research) and as such withholding treatment is considered ethically allowable. I would also want to know how the researchers would deal with infants in the control arm whose mothers were breastfeeding. Presumably, they would not insist that breastfeeding be withheld. In the evaluation of risk, only those risks that are attributable to the research (including cumulative risks) are considered, and they are not compounded with the risks attributable to clinical care.

So I would not be able to vote yea or nay on this protocol without more information. Specifically, the researchers must better clarify their research question and justify their choices for treatment and control groups.

Jenni Linebarger Writes

As recently as 2009, *Pediatrics* published a randomized control trial on the

management of procedural (immunization) pain in newborns that included a “no treatment” arm. In their defense, the authors explained that unfortunately the clinical standard of care is to do these procedures without analgesia, and they suggested that further evidence might change that standard.⁴ Is another study needed? Will more evidence change the standard? Reviewing this protocol today, I ask 3 questions. First, what evidence do we have about treatments for procedural pain in newborns? Second, what evidence do we still need? Finally, what is the current clinical standard of care for the treatment of procedural pain in newborns?

What Evidence Do We Have?

Twenty years have gone by since the publication of the first trial evaluating the analgesic effects of sucrose for procedural pain in newborns. Over the following 10 years, further data collection led the International Evidence-Based Group for Neonatal Pain to publish a consensus statement for the prevention and management of neonatal pain.⁵ And just last year, 2 high-quality reviews on sucrose for analgesia were published.^{6,7}

The first, from the Cochrane Neonatal Group concluded, “The results of the 44 studies in this review provide further evidence supporting the efficacy and safety of sucrose for reducing pain from single and repeated heel lances” (p. 57). Harrison et al⁷ reviewed 125 primary research studies and came to the strong conclusion that “clinical equipoise relating to analgesic effects of sweet solutions no longer exists for single episodes of procedures for healthy preterm and term newborn infants” (p. 894). In short, we have evidence, “high quality, synthesized evidence,” for the efficacy of sucrose for infants during commonly performed painful procedures.

What Evidence Is Still Needed?

There are knowledge gaps to be filled within the field of neonatal pain. Future randomized control trials could assess the “minimum dose” of sucrose needed for effective analgesia or the interaction of sucrose with other behavioral or pharmacologic interventions during more invasive procedures. Studies are also needed to determine the efficacy and impact of sucrose for repeated and/or prolonged use in newborns. And although we should now agree that sucrose does provide effective analgesia for newborns during painful procedures, much remains unknown on the underlying mechanisms of sucrose for pain relief in infants.

What Is the Current Clinical Standard of Care?

In spite of the existing evidence about the efficacy of sucrose, a recent study of European NICUs revealed tremendous practice variation. The percentage of infants who were given sucrose before heel lancing ranged from 5% to 100%.⁸ A Canadian study, published in 2011,

revealed that less than half of NICU patients who underwent painful procedures were given any pharmacologic intervention.⁹ These descriptive studies of current practice suggest that sucrose has been adopted as the standard of care by some NICUs but not by others. Using this evidence, one could argue that infants who are receiving placebo are not being denied standard treatment. Instead, they are being offered the treatment (or non-treatment) that is, in fact, standard in many NICUs today.

This raises a difficult issue. Should the “standard of care” be based on the best available evidence? Or should it be based upon observational studies of what practicing doctors actually do? That question arises in quality improvement programs, in lawsuits, and in the review of research protocols. For research protocols, the answer is, perhaps, easiest: the standard of care should be defined by the best available evidence. The proposed study, as designed, adds nothing to that existing data, and I would not approve it.

John D. Lantos Comments

This case illustrates the tensions in 2 tension-filled domains of controversy: the specific issue of analgesia treatment in neonates and the more general issue of equipoise in randomized clinical trials. The first issue is complicated because pain is subjective. Neonates cannot report their own pain, so all assessments of neonatal pain can be questioned, criticized, and delegitimized. The larger issue in research ethics is when we know enough about an experimental treatment to decide that we no longer need more studies. This issue has arisen with therapies such as antenatal steroids, extracorporeal membrane oxygenation, hypothermia, and nitric oxide. Clinicians, researchers, and IRB members must make judgments about strength of evidence to decide whether a new study, especially a placebo-controlled study, is ethically permissible. The principle is clear. Studies in which subjects are denied access to clearly beneficial standard therapy are unethical. The application of that principle to particular therapies and particular studies is often less clear.

REFERENCES

1. Hatfield LA, Chang K, Bittle M, Deluca J, Polomano RC. The analgesic properties of intraoral sucrose: an integrative review. *Adv Neonatal Care*. 2011;11(2):83–92, quiz 93–94
2. Simons SH, van Dijk M, Anand KS, Roofthoof D, van Lingen RA, Tibboel D. Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. *Arch Pediatr Adolesc Med*. 2003;157(11):1058–1064
3. World Medical Association Declaration Of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 59th Assembly of the World Medical Association, Seoul, Korea, 2008. Available at: www.wma.net/en/30publications/10policies/b3/17c.pdf. Accessed June 14, 2012
4. Bellieni CV, Buonocore G. No analgesia to the control group: is it acceptable? *Pediatrics*. 2010;125(3). Available at: www.pediatrics.org/cgi/content/full/125/3/e709—author reply e709–e710
5. Anand KJ; International Evidence-Based Group for Neonatal Pain. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med*. 2001;155(2):173–180
6. Stevens B, Yamada J, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database of Syst Rev*. 2004;(3):CD001069
7. Harrison D, Bueno M, Yamada J, Adams-Webber T, Stevens B. Analgesic effects of sweet-tasting solutions for infants: current state of equipoise. *Pediatrics*. 2010;126(5):894–902
8. Losacco V, Cuttini M, Greisen G, et al; ESF Network. Heel blood sampling in European neonatal intensive care units: compliance with pain management guidelines. *Arch Dis Child Fetal Neonatal Ed*. 2011;96(1):F65–F68
9. Stevens BJ, Abbott LK, Yamada J, et al; CIHR Team in Children's Pain. Epidemiology and management of painful procedures in children in Canadian hospitals. *CMAJ*. 2011;183(7):E403–E410