

Summary Proceedings From the Neonatal Pain-Control Group

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

Recent advances in neurobiology and clinical medicine have established that the fetus and newborn may experience acute, established, and chronic pain. They respond to such noxious stimuli by a series of complex biochemical, physiologic, and behavioral alterations. Studies have concluded that controlling pain experience is beneficial with respect to short-term and perhaps long-term outcomes. Yet, pain-control measures are adopted infrequently because of unresolved scientific issues and lack of appreciation for the need for control of pain and its long-term sequelae during the critical phases of neurologic maturation in the preterm and term newborn. The neonatal pain-control group, as part of the Newborn Drug Development Initiative (NDDI) Workshop I, addressed these concerns. The specific issues addressed were (1) management of pain associated with invasive procedures, (2) provision of sedation and analgesia during mechanical ventilation, and (3) mitigation of pain and stress responses during and after surgery in the newborn infant. The cross-cutting themes addressed within each category included (1) clinical-trial designs, (2) drug prioritization, (3) ethical constraints, (4) gaps in our knowledge, and (5) future research needs. This article provides a summary of the discussions and deliberations. Full-length articles on procedural pain, sedation and analgesia for ventilated infants, perioperative pain, and study designs for neonatal pain research were published in *Clinical Therapeutics* (June 2005).

www.pediatrics.org/cgi/doi/10.1542/peds.2005-0620C

doi:10.1542/peds.2005-0620C

The views presented in this article do not necessarily reflect those of the Food and Drug Administration (FDA). This article reflects discussions of designing clinical trials in newborns and should not be construed as an agreement or guidance from the FDA. Drug development and clinical-trial review must be discussed with the relevant review division within the FDA.

Key Words

pain, neonate, Newborn Drug Development Initiative, analgesia, anesthesia

Abbreviations

FDA—Food and Drug Administration
NSAID—nonsteroidal antiinflammatory drug
NCA—nurse-controlled analgesia

Accepted for publication Oct 17, 2005

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275); published in the public domain by the American Academy of Pediatrics

BACKGROUND

Since the early 1980s, it has become increasingly appreciated that the fetus and newborn perceive and respond to pain¹⁻⁶ (see Table 1 for definitions). Pain in the newborn is a complex, multilayered phenomenon involving different sources of pain and different types of pain, which can involve various combinations of receptors and mechanisms within the developing nervous system.⁷⁻⁹ Pain can be acute, established, or chronic. Pain can be classified as physiologic, inflammatory, neuropathic, or visceral, with each of these categories further divided according to the degree of severity. Once pain occurs, a series of sequential neurobiological changes take place involving activation and modulation of the pain system. If pain is prolonged or repetitive, the developing pain system may be modified permanently, resulting in altered processing at the spinal and supraspinal levels.^{10,11} Pain is associated with different clinical and neurophysiologic states such as primary and secondary hyperalgesia, in which the processing of noxious stimuli is accentuated and pain is magnified.¹²⁻¹⁵ Over the last several years, evidence from both clinical and preclinical research has shown that newborns are more sensitive to pain than older infants, children, and adults.¹¹

All infants experience pain, but for normal newborns the painful experience is limited to a heel lance or venipuncture for metabolic screening or intramuscular injection of vitamin K or vaccines. For preterm or ill term

neonates, the experience is very different. They are exposed to (1) repeated procedural pain,¹⁶⁻¹⁸ (2) extensive tissue damage resulting from surgery, or (3) the invasiveness of endotracheal tubes placed for mechanical ventilation.¹⁹ Thus, at a time when healthy term infants are learning about their environment and preterm infants are growing in the protective uterine environment, ~8% of neonates are coping with pain that, if left untreated, will interfere with normal growth and development.^{20,21}

In addition to humanitarian concerns, current consensus is that the treatment and/or prevention of pain is considered beneficial and necessary for preterm and term neonates.²²⁻²⁵ Multiple sources of clinical and experimental evidence support the need for providing adequate analgesia/anesthesia for newborns who undergo invasive procedures (medical, surgical, diagnostic, and therapeutic) or develop conditions associated with a significant component of pain (eg, skin burns, necrotizing enterocolitis).^{11,26} Minimal anesthesia during surgery has been associated with an increased incidence of intraoperative and postoperative complications leading to poor surgical outcomes.²⁶⁻³⁰ The consequences of repetitive or prolonged pain in the neonatal period include long-term changes in pain sensitivity and pain processing^{15,31-33} and may be associated with a variety of neurodevelopmental, behavioral, and cognitive deficits that manifest in later childhood.^{20,21,31,34-38} Improved clinical and developmental outcomes highlight the importance of adequate pain control in the human neonate.^{13,31,39-46} Despite this evidence, analgesics are used inconsistently during moderate to severely painful procedures in the newborn period. Studies have documented the vast number of invasive procedures that are performed in newborn infants, often without analgesia.^{17,18,47,48} A 2003 study found that analgesics were used in <35% of the nearly 20 000 procedures performed on 151 neonates.⁴⁷

In February 2003, the Food and Drug Administration (FDA) and the National Institutes of Health established a group of international experts to assess the state of knowledge in the field of neonatal pain. The neonatal pain-control group met regularly to discuss clinical-trial-design issues, drug prioritization, ethical constraints, gaps in knowledge, and future research needs. The group developed manuscripts that address 3 thematic aspects: (1) management of pain associated with invasive procedures; (2) sedation and analgesia during mechanical ventilation; and (3) mitigation of pain and stress responses during and after surgery in newborn infants. These issues were addressed further in a larger meeting, the Neonatal Drug Development Initiative (NDDI) Workshop, which was convened by the FDA and National Institutes of Health in March 2004. Invited expert discussants from outside this group were asked to review and comment on each of these manuscripts, which addressed the state of information in various areas of neo-

TABLE 1 Definition of Common Terms (as They Apply to the Neonate)

Term	Definition
Pain	"[A]n unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" ¹⁵³ (note that the inability to communicate verbally or nonverbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment)
Stress	"[A]n actual or perceived threat that leads to a disturbance of the dynamic equilibrium between an organism and its environment" ¹⁵⁴
Stress response	"[A] response based on the individual's perception of control and predictability of its environment, generally characterized by changes in four primary domains: endocrine, autonomic, ^a immunological, and behavioral" ¹⁵⁵
Analgesia	Absence of pain in response to stimulation that would normally be painful
Anesthesia	Achieving unconsciousness (lack of implicit recall and lack of awareness of surgery), analgesia, suppression of autonomic responses to noxious stimuli, and immobility
Pain control	Diminution in the intensity or duration of pain or both
Sedation	"[A] medically controlled state of depressed consciousness or unconsciousness from which a patient may be aroused, with or without the loss of protective airway reflexes, and a decreased ability to respond appropriately to verbal or painful stimuli" ^{156,157}

^a Autonomic stress responses include hemodynamic, respiratory, and other visceral changes.

natal pain control and clinical-trial–design issues. The following is a brief summary of the salient issues discussed in the March 2004 meeting.

REASONS TO CONSIDER TREATMENT OF PAIN IN NEWBORN INFANTS

Pain in newborn infants is a ubiquitous phenomenon. Newborns in the hospital setting are routinely subjected to painful procedures from very early in their lives. All newborns will experience iatrogenic pain in the first days of life, commencing with vitamin K injection and blood collection for metabolic screening tests before discharge from the hospital.^{17,18,47,48} Additional painful procedures are undertaken in selected populations as warranted by their clinical conditions. In 2000, >1.2 million circumcisions and >200 000 other operations were performed on infants <1 year of age in the United States.⁴⁹ Pain management for these infants often includes the use of systemic, local, and regional anesthetics during intraoperative and postoperative interventions. Because most surgical conditions in the neonatal period require urgent intervention, it is important to develop safe and effective methods of perioperative analgesia and anesthesia.

Neonates who require intensive care, even those at risk for neurologic impairment, may experience 5 to 15 invasive, painful procedures a day.^{18,47,48,50} These procedures may include heel lances, venipuncture, venous or arterial cannulation, tracheal intubation and suction, chest-tube placement, and lumbar puncture.²² Mechanical ventilation is provided to ~35 000 preterm neonates and 20 000 term neonates in the United States each year. Fifty-six percent of infants with birth weights of ≤1500 g are intubated in the delivery room during resuscitation, and 70% of these infants receive assisted ventilation during their hospital stay. As many as 94% of infants of <28 weeks' gestational age are ventilated for a mean duration of 25 days. Repeated exposure to procedural pain experienced by neonates in the neonatal intensive care unit (NICU) is of particular concern, because it occurs at a time when the natural environment for the infant was meant to be the protective intrauterine environment.^{33,51,52}

Multiple lines of evidence have documented the long-term deleterious effects of repeated pain experienced by preterm neonates in the NICU.* Several studies have reported that repetitive painful procedures lead to dampened biobehavioral responses to pain,^{20,31,43,54,55} an indicator of interrupted development, or heightened peripheral sensitivity to pain^{13,56,57} and altered hypothalamic-pituitary-adrenal-axis reactivity.⁵⁸ Animal studies have begun to investigate the mechanisms that underlie the deleterious effects of repeated or prolonged inflammatory pain resulting from invasive procedures.^{52,59–63}

CURRENTLY AVAILABLE THERAPEUTIC OPTIONS

Multiple classes of drugs have been evaluated for the prevention and management of neonatal pain and stress, including opioid analgesics, local anesthetics, general anesthetics, sedatives/hypnotics, nonsteroidal antiinflammatory drugs (NSAIDs), and sucrose. Although much research has been performed with these agents, many questions remain unanswered that prevent the optimal use of these drugs in clinical practice. Within each therapeutic category, the neonatal pain-control group reviewed the published data and identified the gaps in knowledge that should be addressed in future research. Comprehensive current reviews for the management of procedural pain, perioperative pain, and analgesia/sedation for mechanically ventilated neonates, as well as a review focused on clinical-trial–design issues in neonatal pain research, are published separately.

STUDY-DESIGN ISSUES

Procedural Pain

Numerous trials have concluded that analgesics are efficacious for the management of procedural pain in the neonate.²² However, it has been difficult to adopt these interventions in clinical practice because of the numerous limitations of previous research.⁶⁴ The limitations include a lack of information on the efficacy and safety of repeated doses. Because most procedures are recurrent, the repeated use of analgesic interventions in clinical practice may expose neonates to unforeseen risks that are not apparent in single-dose studies.^{65,66} More dose-ranging studies and studies of the pharmacokinetics and pharmacodynamics of repeated doses of analgesics are needed to determine the optimal doses and dosage intervals. In addition, uniform treatment goals and reporting of outcomes are essential so that findings from different studies can be compared. For example, in systematic reviews, only 3 of 38 randomized clinical trials that investigated oral sucrose use⁶⁷ and none of 9 randomized clinical trials that investigated premedications for tracheal intubation⁶⁸ could be pooled for meta-analyses. Standardized treatment goals and reporting of outcomes from future studies will allow meaningful comparisons between studies and pooled data for meta-analyses.

It is unclear whether study findings may be extrapolated among different patient populations and across different procedures. For instance, if an intervention is effective in an older population, does that imply effectiveness in a younger population? In addition, what procedures are considered similar enough so that demonstrated efficacy for one procedure can reliably imply effectiveness for another procedure?

Studies that involve repeated dosing of pain medications during procedures must evaluate the long-term effects of frequent analgesic use compared with the cu-

* Refs 10, 13, 31, 33, 39–42, 44, 46, and 51–53.

mulative risks of repetitive pain on the global development of the child. Because most drugs studied to date involved a single administration, efficacy, safety, and pharmacokinetic studies evaluating repeated use of such drugs in neonatal patients are lacking. Pharmacokinetic studies must be designed to capture the necessary information without causing unnecessary pain or iatrogenic anemia.^{69,70} Finally, it is important to consider the combination of various treatment modalities to maximize their analgesic effects and minimize adverse effects or toxicity.

As a focus for group discussion, 2 hypothetical study designs for procedural pain were presented to evaluate the role of a novel analgesic in the treatment of pain associated with either tracheal intubation or heel lances. Because heel lancing is the most common, painful, invasive procedure performed in the NICU, the group prioritized the clinical trials designed to reduce heel-lance pain in neonates. The group discussed whether placebos should be used for infants who receive no treatment for pain even if no treatment is the current standard of care in some institutions. Sucrose has been described as an effective treatment for infants of >27 weeks' gestational age who are subjected to painful procedures such as heel lances or venipuncture.⁶⁷ Administration of sucrose is not considered a standard of care for all infants who experience procedural pain⁷¹ and is not approved by the FDA, which must be considered if sucrose is compared with other novel therapies for which regulatory approval is sought. Considerable discussion ensued regarding the ethics of designing a study in which neonates undergo an invasive procedure (eg, heel lance) without receiving sucrose or kangaroo care.^{71,72} After much discussion, many workshop participants voiced concern regarding the ethics of testing analgesics against placebo in infants of >27 weeks' gestational age. These issues must be considered further by local institutional review boards, with close monitoring of data and complications by a data-monitoring committee for each study.

Strategies for reducing procedural pain by avoiding or eliminating unnecessary laboratory tests or other interventions^{37,73} (eg, tracheal suctioning, bladder catheterization) and the use of behavioral/environmental approaches (eg, kangaroo care)^{72,74} must be considered. Most of the currently available methods for neonatal pain assessment have been designed and validated for the acute physiologic pain that results from invasive procedures; therefore, these methods should be used as short-term outcomes and for assessing the efficacy of various interventions.⁷⁵⁻⁷⁹ However, there is little consensus on the degree of invasiveness or the intensity or duration of pain caused by different invasive procedures, apart from the broad categories of mild, moderate, or severe pain.^{17,80} Additional studies may allow greater standardization of the intensity and duration of pain

being investigated in randomized clinical trials. Finally, it is important to consider the combination of various treatment modalities to maximize their analgesic effects and minimize the adverse effects or toxicity.⁸¹

Perioperative Pain

Nearly 1.4 million infants in the United States undergo operative procedures each year.⁴⁹ Pain management for these infants must include intraoperative and postoperative interventions. This type of pain has somewhat similar physiologic characteristics that may allow researchers to extrapolate from studies in one patient group to another. Potential drug therapeutic groups include opioids and opioid antagonists, sedatives/hypnotics, vapor anesthetics, local anesthetics, or NSAIDs, and there is opportunity to combine multiple types of analgesic interventions. With treatment courses lasting >5 days, tolerance to and withdrawal from opioid analgesics may occur.⁸²

Study designs for perioperative analgesia, general anesthesia, and regional anesthesia will involve multiple ethical and definitional issues. Before conducting randomized clinical trials for the management of perioperative pain in neonates, we must first decide what constitutes a measure of analgesic efficacy and whether drug efficacy should be a primary outcome measure in neonates and infants. Determining appropriate efficacy or benefit measures is a common problem for the design of all studies on the control of perioperative pain.^{12,76,83-85}

Classic paradigms and study designs for perioperative pain evaluation in adults (pain from third-molar extraction^{86,87}) and older children (using a patient-controlled analgesia device with cumulative morphine use and the opioid-sparing effects as outcomes^{88,89}) are not applicable for the neonatal age group. Creative study designs and novel outcomes, therefore, may need to be considered for studies that investigate neonatal anesthesia or analgesia.²⁷ Patient groups that are easily available for these types of studies might include (1) neonates who are undergoing elective surgeries, (2) infants who are undergoing major abdominal, pelvic, or urologic surgeries, or (3) infants whose respiratory function would allow early extubation after surgery.

The group discussed the merits of a hypothetical study to evaluate the efficacy, safety, and pharmacokinetics of systemic NSAIDs to treat postoperative pain. The study design proposed could be blinded, placebo-controlled, and single- or multiple-dose, with nurse-administered opioids (NCA) for rescue analgesia. Patients in the placebo group may experience moderate pain, but immediate rescue would be available. Participants opined that this approach is ethically justified because opioids have adverse effects, and NCA exposes the patient to less harm with very-low-dose intermittent boluses (if the test drug has an opioid-sparing effect) and the amount of opioid a patient receives can be mini-

mized. A preferred approach is to have the bedside nurse give the NCA bolus based on a pain-score criterion,^{90,91} but an overriding concern is whether NCA based on an observational pain-score criterion has validity.^{76,83,92,93}

Important issues about the study of perioperative pain include whether surrogate measures of efficacy (eg, “opioid sparing” or reducing the need for opioid analgesics) are sufficient, whether one can control for the interactions of the supplemental opioid with the other agent under study, and how to study the efficacy and time course of each incremental dose. Furthermore, standardization of intraoperative management, including (1) intraoperative analgesics, anesthetics, and muscle relaxants, (2) fluid management, (3) glucose infusion rate, (4) body temperature, (5) and the degree of surgical stress⁹⁴ would be critical to the proposed study design. The long-term effects of opioids and general anesthetics are important but difficult to study,⁹⁵ perhaps because of the lack of available cohorts with well-documented neonatal characteristics and standardized therapy in the neonatal period.^{96–98}

Virtually no data exist on a morphine or fentanyl dosing regimen that uniformly relieves pain in nonintubated neonates. Measures of respiratory effect and analgesic efficacy are very different in intubated and nonintubated populations.^{90,99} Future studies should examine the influence of administration of perioperative analgesics on the duration of assisted ventilation required, the timing of extubation, and overall respiratory function.^{100–102}

General anesthesia includes achieving unconsciousness (lack of implicit recall and lack of awareness of surgery), analgesia, suppression of autonomic responses to noxious stimuli, and immobility. Studies using general anesthesia in the pediatric age group need to address whether newer agents are safer in the short-term than existing agents and investigate their immediate and long-term postoperative outcomes. An unresolved question is how to interpret the results from rodent studies that investigate the short- and long-term effects of various combinations of general anesthetic drugs on the developing nervous system.^{96,103} These studies using infant rat pups demonstrate accelerated neurodegeneration after multihour anesthetic administration, with unknown effects on suckling, oxygenation, or blood pressure, and may not be applicable to human neonates and infants. Extrapolation of these rodent data to human neonates is questionable because of interspecies variation, although these studies should provoke clinical investigators to examine the long-term neurocognitive effects of prolonged exposure to anesthetic drugs in preterm and term neonates.^{95,98,104}

For obvious ethical reasons, studies on general anesthesia should not include a placebo group.¹⁰⁵ The efficacy and potency of volatile anesthetics can be determined by defining a minimal alveolar concentration that sup-

presses movement in response to the surgical incision.¹⁰⁶ Important outcome measures to consider would include suppression of movement, intraoperative hemodynamic stability and stress responses, postoperative respiratory function, and time course of recovery.^{30,107} Infants who undergo elective inguinal hernia repairs are suitable candidates to evaluate the efficacy of regional versus general anesthesia.^{108,109}

Pain and Stress Associated With Mechanical Ventilation

Infants are known to perceive pain and experience distress while on mechanical ventilation, particularly resulting from intubations, reintubations, and tracheal suctioning, as well as different types of ventilation.^{110–115} Despite the use of different therapies,^{68,116–120} the precise indications and goals for sedation and analgesia in these neonates remain unclear,¹²¹ and questions about the effects of sedation and analgesia on morbidity, mortality, and brain development have not been answered adequately.^{95,122} Additional research challenges include the need to develop study designs that incorporate the interactions of behavioral and environmental interventions with pharmacologic agents and different types of neonatal ventilation. Furthermore, information is needed on safety, efficacy, drug interactions, pharmacologic tolerance and withdrawal, and pharmacokinetic/pharmacodynamic data associated with the prolonged use of analgesic drugs in these patients. One must consider the lack of validated pain-assessment tools to evaluate ongoing pain and discomfort in mechanically ventilated preterm neonates.^{54,75,76,88,116,123,124}

Numerous randomized, controlled trials have evaluated pain control in mechanically ventilated newborns, but many have been underpowered.^{19,39,102,125–128} Two recent appropriately powered studies enrolled a total of 1048 neonates and demonstrated no differences in the incidence of severe intraventricular hemorrhage, periventricular leukomalacia, or death outcomes between the ventilated infants who received morphine or placebo infusions.^{122,124} Pain assessments during tracheal suctioning were unaltered in 1 trial¹²⁴ and minimally diminished in the other trial.¹²² Future clinical trials using methods to assess ongoing pain will be needed to determine if pain-related outcomes are affected by opioid infusions.

Research questions pertaining to preterm/low birth weight infants requiring mechanical ventilation include:

- Are adverse long-term outcomes reduced by effective analgesia compared with no analgesia?
- Are adverse long-term outcomes altered by effective sedation compared with no sedation?
- Are adverse long-term outcomes reduced by effective analgesia compared with effective sedation?¹²⁹

- Does the combination of analgesia and sedation reduce adverse long-term outcomes?

Options for management of mechanically ventilated preterm newborns include opioids (eg, morphine, fentanyl, others), NSAIDs (eg, ketorolac, ibuprofen lysine), ketamine, and acetaminophen for analgesia and benzodiazepines (eg, midazolam, lorazepam), barbiturates (eg, phenobarbital, pentobarbital, others), hypnotic agents (eg, ketamine, propofol, others), and various other drugs for sedation.¹³⁰ In this age group, drug classes such as the benzodiazepines are used for their sedative effects rather than their anxiolytic properties. Ventilated infants may show signs of agitation, but it is unclear whether this results from anxiety (as in adults) or other causes.^{11,15,19–23,31} Intravenous NSAIDs may be considered as a reasonable alternative to opioid therapy, because they may provide effective analgesia in newborns, spare the use of opioids, and obviate the potential for tolerance. NSAIDs have been used extensively for patent ductus arteriosus closure¹³¹ and intraventricular hemorrhage prevention in preterm neonates, and they have defined pharmacokinetic/pharmacodynamic profiles.^{132–135} However, the analgesic effects of NSAIDs have not been documented in preterm neonates, and the adverse effects of prolonged NSAID therapy can potentially lead to circulatory, renal, hepatic, gastrointestinal, and hematologic complications.¹³⁴ These potential complications may be especially problematic in neonates who are exposed to prolonged stress in the NICU and those who experience rapid changes in maturation of renal function.

Outcome Measures

Neonates cannot report pain or discomfort in the same way that older children or adults can. Therefore, many of the standard study instruments used for measuring the efficacy of analgesia or defining the goals of sedation or analgesia cannot be applied in this population.¹²³ The

neonatal pain-control group discussed the difficulties of using pain-assessment scales. Many studies on methods for evaluating pain or distress in neonates have examined behaviors, physiologic parameters, and other variables as responses to pain. Because many of the pain-assessment methods used for neonates do not have the same scaling properties as the pain measures used for adults,¹³⁶ it is unclear how to use these measures as a basis for clinical intervention or how they relate to improved outcomes.^{122,124} Many neonatal pain scales differ from those used in older patients by including physiologic and not just behavioral parameters.

A number of scales for measuring neonatal pain have been designed and validated to varying degrees. The most commonly used measures are presented in Table 2. Although one might wish to have a single, validated scale for use in the newborn period, it may not be feasible, because the manifestations of pain will differ across the different types of pain, the intensity or duration of pain, and the spectrum of gestational ages.^{75–79,137} Thus, it may be impractical to develop a universal scale for assessing pain in all newborns. If a small number of scales are used extensively, comparing studies and undertaking meta-analyses are facilitated and have more validity. One can also measure the infant's response to next handling when considering the time to recover from an invasive procedure. Because current assessment tools mostly use similar or overlapping parameters, other assessment approaches such as changes in intracranial pressure (measured at the anterior fontanel),^{138–141} palmar sweating (or skin conductance),^{142–145} thresholds for the dorsal cutaneous flexion reflex or abdominal skin reflex,^{12,84,146,147} cerebral blood flow, processed electroencephalogram or event-related potentials measured by detailed electrical mapping,^{148,149} or neuroimaging techniques such as functional MRI^{150,151} need additional development and testing in the newborn.

TABLE 2 Commonly Used Measures of Pain in Neonates

Measure	Variables Included	Type of Pain	Psychometric Testing
PIPP (Premature Infant Pain Profile) ¹⁵⁸	Heart rate, oxygen saturation, facial actions; takes state and gestational age into account	Procedural, postoperative (minor)	Reliability, validity, clinical utility well established
NIPS (Neonatal Infant Pain Score) ¹⁵⁹	Facial expression, crying, breathing patterns, arm and leg movements, arousal	Procedural	Reliability, validity
NFCS (Neonatal Facial Coding System) ¹⁶⁰	Facial actions	Procedural	Reliability, validity, clinical utility, high degree of sensitivity to analgesia
N-PASS (Neonatal Pain, Agitation, and Sedation Scale) ¹⁶¹	Crying, irritability, behavioral state, facial expression, extremity tone, vital signs	Postoperative, procedural, ventilated	Reliability, validity, includes sedation end of scale, does not distinguish pain from agitation
CRIES (Cry, Requires oxygen, Increased vital signs, Expression, Sleeplessness) ¹⁶²	Crying, facial expression, sleeplessness, requires oxygen to stay at >95% saturation, increased vital signs	Postoperative	Reliability, validity
COMFORT Scale ^{92,163–165}	Movement, calmness, facial tension, alertness, respiration rate, muscle tone, heart rate, blood pressure	Postoperative, critical care, developed for sedation, recently validated for postoperative pain in 0- to 3-year-old infants ⁹⁹	Reliability, validity, clinical utility

There is a need to determine what constitutes a minimum clinically important reduction in pain response in neonates.¹³⁶ The conventional figure used to judge whether an agent is effective is its ability to decrease pain by 20% compared with placebo. Preliminary results from a survey of parental and nursing opinions of the minimum clinically important difference in pain response required before using a pain-decreasing intervention in neonates is 15% to 20%.¹⁵²

The group also discussed concerns regarding sample-size issues and the definition of a meaningful treatment effect. The minimal clinically important difference for an individual may not be the same as for the population. Another approach for sample-size estimation would be to determine a meaningful change in the number of patients who reach a minimally important difference in pain. Alternatively, it might be possible to define a “success” with respect to the ability to achieve a certain response (or nonresponse) in relationship to predefined procedures and stimuli, which would be in contrast to a responder analysis that takes a time-averaged pain score over an extended period of time.

The group discussed the merit of a composite score versus separate scores for behavioral responses and physiologic reactivity in the pain-assessment scales. Adult studies suggest that even when people are behaviorally calm while sedated for invasive procedures, physiologic reactivity to tissue damage still occurs; therefore, behavioral indicators should be kept distinct from physiologic indicators. Total scores obtained from a composite scale, however, do not differentiate between these parameters, which can be misleading. It may be possible to design a composite measure with behavioral, physiologic, or biochemical subscales as long as there is internal consistency within the measure and each subscale makes independent contributions to the construct of pain or its intensity or quality. Another concern was that different kinds of indicators may not be correlated across the entire range of responses or across different age groups or patient populations with different diseases.

It was also recognized that at present there are considerable limitations to assessing pain objectively in the newborn period. It is difficult even for trained nursing personnel to accurately assess pain as evidenced by the frequent use of supplemental pain medications given to both treatment groups in placebo-controlled trials.^{122–124}

ETHICAL ISSUES

Unlike studies conducted in adults, clinical trials involving neonates face the ethical constraint of the inability to incorporate a placebo that withholds analgesia for any length of time. The key ethical questions discussed by the neonatal pain-control group concerned the appropriateness of using placebos in different circumstances. One topic of discussion was the lack of a clear “standard of care” or widely accepted practice for treatment of

neonatal pain. This issue raises special problems in clinical trials, because equipoise (ie, a genuine state of uncertainty between 2 treatments, the ethical precondition of a justifiable randomized, controlled trial) is difficult to achieve when not much is known about either treatment in a randomized clinical trial. It is unclear what the “standard” care ought to be for infants whose parents do not agree to participate in the trial. For example, a sucrose versus topical anesthetic study to evaluate efficacy in the treatment of heel-lance pain is designed to look like a standard versus experimental-study design, but there is no standard of care in this clinical situation; one is comparing a therapeutic agent with another, and every drug used is “off-label.”

Two decision-making heuristics might be used to resolve this dilemma. First, one could look at current standard practice. If standard practice is to provide no treatment for pain control, then a placebo might be considered ethically acceptable. Thus, if most people do not use sucrose before a heel lance, then it would be permissible to test topical anesthetics against placebo. The second heuristic would be to determine if there is a proven effective and safe means of pain control for a particular indication in a particular population. If so, then a placebo-controlled trial would be unethical. Instead, any new treatment must be tested against the known efficacious treatment even if it is not necessarily the usual and customary treatment. Another possibility is that the new therapy is “add-on” (eg, the topical local anesthetic could be added on to another “standard” therapy such as sucrose), which allows all subjects to receive the “standard” therapy.

A placebo-controlled design might be considered ethical even when analgesia and sedation are considered standard of care or when an approved drug is available, for example, when adequate provision for rescue medication is provided. Even in a longer-duration trial (eg, ICU sedation), randomized withdrawal designs (ie, one arm continues on active and another arm receives placebo) with provision of rescue medication might be acceptable ways to achieve a demonstration of efficacy that might also be considered ethical.

Specific ethical challenges include the need to explain why the research is appropriate and why the risks of analgesia are acceptable. The simple answer is that pain is bad, and analgesia may be able to control it; therefore, a study is reasonable and ethical. An important ethical question is: Why is a control group acceptable if pain is bad and analgesia is good; why not just use analgesia? One might respond to this question by stating that, at present, we are uncertain whether any treatment really has benefits that are objectively measurable, given the inaccuracy of current assessment methods. The short-term measures of benefit are ambiguous, and there is disagreement regarding which measure is most relevant for the short-term or suitable as a surrogate measure for

long-term outcomes. Uncertainty exists about the short-term and long-term risks of treatment.

A realistic goal would be to develop a specific trial design with defined risks, benefits, and outcomes and then define the ethical justification for the study in language suitable for nonmedical personnel to appreciate the dilemma. Developing standard informed-consent language is advisable. However, this method has been tried and does not work well, because the opinions of institutional review boards are not uniform across the country. If, however, regulatory agencies collectively agreed on a particular language to describe studies of neonatal analgesia, local institutional review boards may feel more comfortable in approving such studies.

The fundamental paradox of pediatric research is that unapproved and unstudied drugs are used in clinical care; however, for clinical research, regulatory mandates govern these studies. In the latter case, investigators may face some regulatory hurdles as discussed below. Ethical constraints that need to be considered in the design of pain studies include the following potential risks to the patient:

- withholding of analgesia in placebo-controlled trials;
- unknown adverse effects that have not been seen or documented in older children or adults;
- burdens related to monitoring for routine laboratory tests and pharmacokinetic studies; and
- potential for invasive sampling.

REGULATORY CONSIDERATIONS

The FDA requires greater clarity on the specific indication being sought for a pain-indication labeling in the neonatal population. An indication describes the treatment, prevention, or diagnosis of a recognized clinical disease or condition or of a manifestation or symptom of the disease or condition. The indication should be associated with well-identified populations, clinical settings, and clinical outcomes and goals that are related to a clinical benefit.

To make a risk-benefit assessment and decide whether to grant an indication, the benefits and risks should be clearly discernable and supported by substantial evidence of effectiveness based on adequate and well-controlled studies. For example, scientists and clinicians may deem a change in pain-assessment score in itself as a meaningful clinical benefit. However, it may be necessary to quantify further the degree and duration of change considered to represent a meaningful clinical benefit. In evaluation of analgesic trials, the FDA evaluates such parameters as the duration of action and time to onset of action. Thus, if these variables can be assessed in the study population, they are important features for describing dosing interval. Additional information that is critical to achieving regulatory approval is thorough

characterization of safety and pharmacokinetics. Drugs or interventions that are unapproved by the FDA can be used in a clinical trial provided that evidence is available to support the safety of the trial in the study population and that the protocol is written to ensure the safety of enrolled subjects. A regulatory hurdle is that studies that use an unapproved drug or intervention may not be appropriate to support a regulatory approval. However, if an unapproved intervention or drug that is considered a standard of care is used as a comparator therapy in a trial, then a superiority trial design may warrant consideration.

GAPS IN KNOWLEDGE AND FUTURE DIRECTIONS FOR RESEARCH

There are gaps in knowledge and issues in pain assessment and therapy that need additional research. These needs include:

- development and/or validation of new or existing methods of pain assessment for neonates of varying gestational ages, especially extremely preterm neonates (23–26 weeks' gestational age) or neonates at high risk for neurologic impairment;
- development of pain-assessment scales for preterm and term neonates with ongoing pain or chronic pain;
- determination of a gold standard for pain measurement for neonates;
- determination of the short- and long-term goals of analgesia and sedation (How should changes in pain or sedation scores be interpreted to conclude clinical benefit? What is the nature and magnitude of benefit to be targeted to determine if the risk is justified by the benefit?);
- greater understanding of the ontogeny of the physiologic and behavioral responses to pain in neonates (What are the regulatory mechanisms for the development of autonomic and stress-responsive systems, and how are these altered by inputs from the pain system? Do the patterns of pain responses in early life determine adult pain processing or susceptibility to chronic pain disorders in later life?);
- use of noninvasive measures of pain to study specific components of the central nervous system (ie, autonomic nervous system function) that are thought to be altered by both early pain and/or analgesic exposure (Are there patterns of response that enable us to identify physiologic reactivity profiles that are more informative than single outcomes alone?);
- evaluation of whether poorly treated pain during the neonatal period leads to long-term adverse outcomes in higher cortical functions, such as various components of executive functions and other domains, as

have been demonstrated in human cohort studies and in experimental animals;

- investigation of the feasibility and utility of neuroimaging studies for pain in preterm and term infants using functional MRI, electroencephalogram monitoring, event-related potentials, and/or near-infrared spectroscopy;
- determination of the pharmacokinetics and pharmacodynamics of all analgesic drugs used in neonates after single and repeated doses, as clinically warranted, and including the various formulations intended to be used clinically for each compound;
- determination of the optimal approach for pharmacokinetic studies, including age groups to be investigated, blood-sampling strategies, and microassay techniques (eg, sparse and random blood sampling from a large number of infants may be analyzed by using population pharmacokinetic approaches such as nonlinear mixed-effect model (NON-MEM), nonparametric expectation maximization (NPEM), or other programs);
- evaluation of the various combinations of pharmacologic agents or combined effects of pharmacologic as well as behavioral and environmental approaches for pain management in neonates (for combined drug therapies, there may be consideration for the use of different classes of drugs systemically [oral/intravenous] or for spinal/epidural/nerve-block techniques to minimize adverse effects and maximize analgesic efficacy);
- determination of the effects of analgesic drug exposure on long-term global developmental outcomes (ideally, developmental outcomes should be domains that reflect neurotransmitter systems [monoamines, opioid systems, etc] that might be altered by such drugs; domains of interest might include state regulation [arousal, attention, behavioral control, orientation], executive function [active working memory, inhibitory control, planning and capacity to shift strategies], organization [temporal-sequential ordering, spatial ordering], and memory, learning, consolidation, language, and neuromotor skills);
- investigation of the factors underlying biological variation in pain responses and analgesic safety and efficacy, including the use of pharmacogenetic (phenotype → genotype) and pharmacogenomic (genotype → phenotype) analyses to identify populations with distinct responses to pain (acute responses, long-term neurodevelopmental changes) or analgesia (efficacy, adverse effects, tolerance), as well as emerging neonatal capacities to metabolize analgesics (eg, developmental role of hepatic isoenzymes in the cytochrome P450 system); and

- pharmacoeconomic analyses of pain management in the neonate, such as cost-utility and cost-effectiveness analyses.

SUMMARY

Neonatal pain management stands at the threshold of momentous change and great opportunity for making fundamental scientific and major clinical advances in the next few years. To exploit this potential, (1) findings from previous studies need to be assimilated and consolidated, (2) novel approaches for pain assessment must be investigated, (3) the importance of short-term and long-term clinical outcomes needs to be defined, (4) relevant outcomes and their surrogate markers need to be developed,⁵ ethical and regulatory needs should be addressed, and (5) clinical trials using the currently available and newer pharmacologic agents must be designed, perhaps by using novel study designs. Additional studies in preterm neonates, for example, must devise ways to distinguish the effects of multiple factors that cause prematurity and differentiate the incident factors associated with immaturity from the effects of repetitive neonatal pain. Essential requirements include a well-designed study with detailed data collection, clear establishment of a pretreatment baseline, selection of outcome measures that are reliable and easily measured with uniform consistency across centers, and measures that are easily correlated among different study sites. Such a study would incorporate appropriate statistical techniques to discern the effects of confounding variables. An ideal protocol for evaluating drugs would include validated pain-assessment instruments for the particular circumstance and age group, stress markers, DNA sampling, evaluation of drug disposition, and neurophysiologic measurements.

Gaps in knowledge exist about pain perception and the morphologic substrate, the relationship between neurophysiologic parameters and pain assessment, sensitization after repeated painful stimuli, mechanisms of tolerance and withdrawal, and the correlation between pain-assessment instruments and plasma levels of analgesics. In addition, clinical trials are needed to evaluate the effect of pain management on long-term outcome measures in neonates and young infants.

The current state of knowledge for neonatal pain management at this workshop revealed many questions that need additional investigation or extension to other infant populations. Critical needs identified include (1) refinement of pain-assessment scales such that their value and limitations during different applications is better understood, (2) development of new and innovative pain-assessment technologies that incorporate reproducible physiologic variables with a high degree of specificity, (3) assessment of the adequacy of existing literature on the pharmacokinetics and pharmacodynamics of key medications, (4) improved education of health care per-

sonnel to use currently available pain-reduction methods, and (5) additional discussion of the ethical aspects of pain studies in the neonatal period and incorporation of innovative study designs. It is hoped that the outcome of these discussions will encourage the scientific community to focus studies in this important area of pediatric care and assist the regulatory and funding agencies to develop appropriate initiatives.

ACKNOWLEDGMENTS

We gratefully acknowledge financial and administrative support from the National Institutes of Health and the US Food and Drug Administration. Dr Anand received funding from the National Institute of Child and Human Development (grant R01 HD36484) during this period.

We thank the reviewers for their helpful comments: Nancy Chang, MD, US Food and Drug Administration; William Oh, MD, Women and Infant's Hospital of Rhode Island; Arne Ohlsson, MD, MSc, Mount Sinai Hospital; Bonnie Stevens, PhD, RN, Hospital for Sick Children; and Dick Tibboel, MD, PhD, Sophia Children's Hospital.

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Pediatrics 2006;117;S9

DOI: 10.1542/peds.2005-0620C

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