



eNeonatal Review

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Awareness of the importance of recognizing and treating pain in all age groups has gained prominence in recent years. Because the interpretation of pain is subjective, there has historically been a lack of recognition of pain in neonates. Sick neonates who require intensive care are more likely to undergo repetitive painful procedures, and may lack traditional behavioral responses to pain, such as crying and grimacing, due to their underlying illness. This problem is further compounded in low birth weight infants who may be developmentally more vulnerable to the effects of pain.

Despite improved awareness of neonatal pain and the development of neonatal pain assessment tools, controversy remains over how best to recognize and treat pain. Improved attention has been made to the NICU environment, with efforts to minimize noxious stimuli such as noise, light and excessive handling, but infants still undergo painful procedures without adequate analgesia. The controversy is fueled by concerns regarding the safety of the treatment modalities and limited long term follow up.

In this month's issue, we provide a wide-ranging review of the data exploring the recognition of pain, analgesic modalities, and long-term outcomes in the neonate population.

Reviews

Anne-Lise Yohay M.D.

Commentary:

Susan W. Aucott, M.D.

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Guest Editors of the Month

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Guest Faculty Disclosure

Susan W. Aucott, M.D.

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Anne-Lise J. Yohay, M.D.

Faculty Disclosure: No relationship with commercial supporters

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COMMENTARY

Treatment of pain in neonates is often limited by concerns of adverse reactions, or potential long-term detrimental effects. The American Academy of Pediatrics and the Canadian Paediatric Society issued a consensus statement emphasizing the association of pain in the neonatal period to increased morbidity and different responses to subsequent pain¹. They stress the need to consistently assess infants for pain, reduce exposure to noxious stimuli, and adequately treat pain. Similarly, the International Evidence-Based Group for Neonatal Pain published a consensus statement emphasizing the importance of recognizing, minimizing exposure, and treating neonatal pain, and put forth treatment recommendations².

Sucrose has been documented to reduce pain and distress in newborns, and is thought to be mediated through the release of endogenous opiates³. The efficacy in healthy term infants is well documented for isolated procedures such as heel lance and venipuncture. The article by Acharya and colleagues shows that it is also effective for healthy pre-term infants. Unfortunately, the majority of the painful procedures are done repetitively on ill infants. Safety of the use of sucrose for multiple procedures over time has not been well established. The concern of potential adverse neuro-developmental outcome is raised by Johnston and colleagues, although follow up past 40 weeks has not been examined.

Opiates are commonly used for the treatment of acute and chronic pain in sick neonates. It has been postulated that a reduction in the pain and stress experienced by the neonate would not only improve immediate neonatal outcomes, but would impact long-term neuro-developmental outcome. The NOPAIN trial presented pilot study data suggesting that the routine use of morphine infusions in ventilated preterm infants reduced the incidence of poor neurologic outcome, as measured by neonatal death, severe intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL)⁴. These implications led to the Anand, Simons, and Lago trials that showed no improvement of neurologic outcome, and suggested an increase in severe IVH in infants receiving bolus morphine. Fentanyl infusions have shown efficacy in reducing stress, with no impact on clinical outcomes. All these studies conclude that routine use of opiates in ventilated preterm infants is not warranted - rather, treatment should be focused on evidence of pain.

Data on long term outcomes in infants exposed to opiates remains limited. Concerns of potential toxic effects of morphine on the developing brain have been raised in animal studies, and an increase in apoptosis has been seen in fetal neuronal cell culture. While the article by Macgregor and colleagues does not show adverse outcomes in neurodevelopment at 5-6 years, the numbers are small.

The relationship between exposure to pain as a newborn and long term perception of pain has been more clearly delineated. The Buskila and Grunau articles review the lower pain thresholds seen in older children, and higher stress responses at age 8 months, as they correlate to higher numbers of skin-breaking procedures as neonates. Neither study was able to demonstrate a relationship with morphine dosing. In animal studies such as the article by Bhutta and colleagues, the abnormalities in pain perception in the adult animals exposed to neonatal pain were ameliorated by treatment with morphine.

When caring for sick neonates, we are left with the challenge of improving our assessment and recognition of pain in order to better prevent and treat it. Behavioral and pharmacologic treatment of increased pain scores, as well as pre-emptive treatment for procedures known to cause severe pain, will help ameliorate adverse stress responses of the infant. Ongoing research into identifying optimal medications and dosing regimens is crucial in order to maximize the benefits of pain management while minimizing its adverse effects. Additionally, the long-term outcome, for both neurodevelopment and pain perception, should remain a vital component of ongoing research efforts.

References:

1. American Academy of Pediatrics and Canadian Paediatric Society. [Prevention and management of pain and stress in the neonate.](#) Pediatrics. 2000;105:454-461
2. Anand KJS, International Evidence-Based Group for Neonatal Pain. [Consensus statement for the prevention and management of pain in the newborn.](#) Arch Pediatr Adolesc Med. 2001;155:173-180
3. Blass EM, Hoffmeter MA. [Sucrose as an analgesic for newborn infants.](#) Pediatrics 1991;87:215-218
4. Anand KJS, McIntosh N, Lagercrantz H, Young TE, Vasa R, Barton BA. [Analgesia and sedation in preterm neonates who require ventilatory support: Results from the NOPAIN trial.](#) Arch Pediatr Adolesc Med. 1999;153:331-338

RECOGNITION OF PAIN

Simons SHP, van Dijk M, Anand K, Roofthoof D, van Lingen R and Tibboel D. Do We Still Hurt Newborn Babies? *Arch Pediatr Adolesc Med.* 2003; 157: 1058-64.

A Dutch prospective study assesses painful procedures vs. analgesia.

Assessing 151 neonates in the largest NICU in the Netherlands, this study determined the number of painful procedures, attempts at painful procedures, and amount of analgesics administered for any of the painful procedures during the infants' first 14 days of life. 34 painful procedures were evaluated, which ranged from minimally painful procedures (e.g. removal of nasogastric tubes, nasal cannulae placement and x-rays), to moderately painful procedures (e.g. removal of IV cannulae, insertion of nasogastric tubes and enemas), to severely painful procedures (e.g. intubation, arterial line insertion and chest tube insertion). Procedure pain severity was determined by 148 nurses and physicians scoring each procedure on a 0-10 pain scale. Moderate to severely painful procedures were defined as >4 on the 0-10 analog scale, and meet the criteria for analgesic administration. It should be noted that the authors did not score infant pain directly.

Gestational age of the infants ranged from 25.3-42 (mean 32.4) weeks with mean birth weight 1734g. 104 of the 151 infants were premature. The mean NICU stay was 9.1 days. A total of 19,674 painful procedures were performed/attempted, with the majority (63.3%) suctioning procedures. Each infant underwent an average of 14.3 procedures per day, with most procedures occurring on the first NICU day. 32.5% of infants received analgesia (morphine or acetaminophen) on day one compared to 14.6% on day 14. Approximately 40% of infants received no analgesia during the study.

The authors conclude that only a third of NICU patients are receiving appropriate analgesia for painful procedures.

However, the authors did not evaluate pain in the infants with available pain scales, using instead scores provided by nurses and physicians which may be less accurate than direct observation of patients. In addition, some of the "painful" procedures chosen may not have been painful enough to warrant analgesia. It would be interesting to look at the severely painful procedures alone and assess the use of analgesics in these cases. Overall, it is important that we look at the number of potentially painful procedures performed and consider our methods of pain control. This article is a start to opening our eyes to this critical issue.

Simons SHP, van Dijk M, Anand K, Roofthoof D, van Lingen R and Tibboel D. Do We Still Hurt Newborn Babies? *Arch Pediatr Adolesc Med.* 2003; 157: 1058-64.

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TREATMENT MODALITIES: SUCROSE IN FULL TERM INFANTS

Overgaard C., Knudsen A. Pain -Relieving Effect of Sucrose in Newborns During Heel Prick. *Biol Neonate.* 1999; 75: 279-284.

Assessing the analgesic effect of sucrose in full term infants.

This prospective, randomized, double-blind study evaluated the effect of sucrose on pain relief during heel sticks in full term infants. Ninety-six healthy and vaginally born infants were observed by videotape during PKU testing on DOL 5-10 after receiving 50% sucrose or water. They were

scored using the neonatal infant pain scale (NIPS) before, during and after the procedure. The duration of crying time was also calculated for each infant. Parents were asked to console their infants during the procedure.

The sucrose group had lower NIPS scores and decreased crying duration versus placebo. Heart rates and oxygen saturations did not differ between the two groups. Low NIPS scores before the procedure predicted decreased pain and reduced crying time during and after the procedure. Sucrose augmented this effect.

This study supports the use of sucrose and parental comforting for pain relief during brief procedures. However, while the results are useful for healthy term infants, they may not apply to pre-term and term infants requiring intensive care.

Overgaard C., Knudsen A. Pain -Relieving Effect of Sucrose in Newborns During Heel Prick. Biol Neonate. 1999; 75: 279-284.

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TREATMENT MODALITIES: SUCROSE IN PRE-TERM INFANTS (1)

Acharya AB, Annamali S, Taub NA, Field D. Oral Sucrose Analgesia for Preterm Infant Venipuncture. Arch Dis Child Fetal Neonatal Ed. 2004; 89: F17-F18.

Assessing the analgesic efficacy of sucrose in pre-term infants.

This randomized, double blinded, placebo controlled, crossover study assessed the efficacy of 25% sucrose oral solution on pain reduction during venipuncture in preterm infants. Thirty-nine < 37 week infants were observed for 2 venipunctures, one after sucrose and one after water. Only non-ventilated infants on room air receiving full feeds without \geq grade II IVH, a history of opiate exposure, dysmorphism or neuromuscular dysfunction were included. The infants were videotaped before, during and after the venipuncture and observed for heart rate and oxygen saturation. Two blinded observers scored the videotapes with the neonatal facial coding system (NFCS) and timed each infant for cry duration.

The mean increase in heart rates was lower for the sucrose group. After sucrose, infants cried for shorter durations and their NFCS scores were lower versus after receiving placebo.

This study reports a potentially useful method for alleviating pain during short procedures for a small population of well preterm infants. Unfortunately, due to their clinical status, sucrose is not practical for all preterm infants. The population studied was well and presumably under low stress at baseline. It does not address the efficacy of sucrose for a painful procedure in an already stressed infant.

Acharya AB, Annamali S, Taub NA, Field D. Oral Sucrose Analgesia for Preterm Infant Venipuncture. Arch Dis Child Fetal Neonatal Ed. 2004; 89: F17-F18.

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TREATMENT MODALITIES: SUCROSE IN PRE-TERM INFANTS (2)

Johnston CC, Filion F, Snider L, et al. Routine sucrose analgesia during the first week of life in neonates younger than 31 weeks postconceptional age. *Pediatrics* 2002;110:523-528

Assessing sucrose analgesia and neuro-developmental outcomes.

This prospective, randomized, double blind controlled trial assessed 103 preterm infants at 3 level III NICU's. Preterm infants born at <31 weeks gestation were enrolled within 48 hours of life and randomized to receive sucrose (0.1 cc of 24%) or sterile water orally up to 3 times 2 minutes apart for every invasive (skin-breaking) or uncomfortable (eg endotracheal suctioning, gavage tube insertion) procedure for a 7 day period. A subset of infants were evaluated for analgesic effect with the Neonatal Facial Coding System. The study's primary focus was neuro-developmental outcome, as assessed by the Neurobehavioral Assessment of the Preterm Infant (NAPI) at 32, 36 and 40 weeks post conceptional age.

The number of sucrose/sterile water doses per infant during the week ranged from 24-125, with a mean of 63 in the sucrose group and 58 in the control. Serum glucose levels were not different between the groups. In a subset evaluation, the sucrose provided effective analgesia, even on day 7.

No significant differences were found on the NAPI between the sucrose and control group. A regression analysis done to examine the influence on the number of doses of sucrose showed fewer doses of sucrose predicted improved development in the motor subscale. Although the authors caution that the study was not powered for this analysis, it does raise concern about the safety of repetitive doses of sucrose in this vulnerable population.

Johnston CC, Filion F, Snider L, et al. Routine sucrose analgesia during the first week of life in neonates younger than 31 weeks postconceptional age. *Pediatrics* 2002;110:523-528

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TREATMENT MODALITIES: MORPHINE

Anand KJS, Whit Hall R, Desai N, et. al. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomized trial. *Lancet*. 2004; 363:1673-1682.

Simons SHP, van Dijk M, van Lingen RA, et. al. Routine Morphine Infusion in Preterm Newborns Who Received Ventilatory Support, a randomized controlled trial. *JAMA*. 2003; 290:2419-2427.

Two studies assess the effects of morphine use in neonates.

Anand (et al) conducted a prospective, multi-center, randomized, double blinded, placebo-controlled study to examine the effect of continuous morphine analgesia in 23-32 week gestation infants on the composite outcome of neonatal death, severe intraventricular hemorrhage (IVH, grade III-IV) and/or periventricular leukomalacia (PVL) and on the individual outcomes of death, IVH and PVL. There were 449 infants in both the placebo and morphine groups, with the morphine group subdivided to receive 3 different doses based on gestational age. Infants in each group received a 100 μ g/kg loading dose followed by 10 μ g/kg/hr at 23-26 weeks gestation, 20 μ g/kg/hr at 27-29 weeks gestation or 30 μ g/kg/hr at 30-32 weeks gestation for 14 days. Open label

morphine was given based on clinical judgment. Cranial ultrasounds were performed at 4-7 days and again at 28-35 days for infants born at <30 weeks gestation and at 14-28 days for infants born at 30-32 weeks gestation.

There were no differences in outcome between the placebo and morphine groups. However, when the groups were stratified for gestational age, there was a higher percentage of severe IVH in the 27-29 week infants who received morphine. The authors suggest that the higher morphine dose in the 27-29 week group may have caused more hypotension and, thus, contributed to the increased rate of IVH in this group.

The authors then compared infants in both groups who did and did not receive any open-label morphine. Infants receiving open label morphine in both the placebo and morphine groups had higher death, IVH and PVL outcomes. Infants in the morphine group who did not receive open label morphine had significantly more IVH but no increase in death or PVL. However, when the authors excluded all infants who were hypotensive prior to the start of the study drug, there were no significant differences between the non-open label morphine groups for any outcomes. Additionally, infants in the morphine group were more likely to be hypotensive.

Premature infant pain profiles (PIPPs) were done before starting the study drug/placebo, again at 24 and 72 hours after starting it, and again after the study drug/placebo was weaned. The morphine group had significantly lower PIPP scores only at the 24 hour time point. Infants in the morphine group also received mechanical ventilation for a longer time period and spent more time getting to full feeds versus the placebo group.

The authors conclude that standard morphine infusions in preterm ventilated infants do not decrease the frequency of severe IVH, PVL or neonatal death. Intermittent bolus doses of morphine may be detrimental, or may merely be markers for infants who have already suffered neurological damage or who are more medically unstable. It is interesting that although pain scores are lower in the morphine group only at 24 hours, the time to full feeding and extubation are delayed in the morphine group.

Simons (et al) conducted a prospective, randomized, double-blind, placebo-controlled two-center study in 150 preterm and term ventilated infants to determine the effect of continuous morphine infusion on pain scores, the incidence of IVH and poor neurologic outcome (severe IVH, PVL or death). The infants received a 100g/kg load followed by 10g/kg/hour morphine or sodium chloride infusion. The infusions were continued for up to 7 days. Open label morphine was given based on clinical judgment. The bedside nurse scored the infant's pain with the visual analog scale (VAS) before, during and after ETT suctioning twice daily. Infants were videotaped during these procedures for later scoring with the NIPS, PIPP and VAS scales. IVH and PVL were diagnosed by cranial ultrasound using standard criteria.

For all pain scores, there were no differences between the morphine and placebo groups. Poor neurologic outcome was not associated with morphine infusion. However, the incidence of all grades of IVH (mostly low grade IVH) was higher in the placebo group (OR=2.36).

The latter finding is interesting in light of the Lancet 2004 study involving one of the same authors (Anand), where the incidence of severe IVH was higher in the 27-29 week subgroup who received 20 μ g/kg/hour of morphine. In this JAMA 2003 study, however, the IVH is mostly low grade and of unclear long term significance.

Anand KJS, Whit Hall R, Desai N, et. al. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomized trial. *Lancet*. 2004; 363:1673-1682.

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Simons SHP, van Dijk M, van Lingen RA, et. al. Routine Morphine Infusion in Preterm Newborns Who Received Ventilatory Support, a randomized controlled trial. *JAMA*. 2003; 290:2419-2427.

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TREATMENT MODALITIES: FENTANYL

Lago P, Benini F, Agosta C, Zacchello F. Randomised controlled trial of low dose fentanyl infusion in preterm infants with hyaline membrane disease. *Arch Dis Child Fetal Neonatal Ed*. 1998; 79: F194-F197.

Assessing the risks/rewards of continuous infusion fentanyl.

The Lago et al. study is a randomized, prospective, blinded, single-center trial assessing the effects of continuous fentanyl infusion in 26-32 week premature infants with RDS on their behavioral and neuroendocrine stress responses. Fifty-three ventilated infants were assigned to fentanyl infusion (0.5-2 μ g/kg/hr titrated to keep the infant sedated but arousable) or no infusion. Once the infants approached extubation, the fentanyl was weaned over 24 hours. Behavioral sedation scores (Hartwig) were done every 2 hours by a nurse blinded to treatment, then summed and compared at 24 hour intervals. Metanephrine and normetanephrin/creatinine ratios were measured at three 24 hour intervals after the start of the fentanyl infusion.

The fentanyl group had lower behavioral sedation scores (i.e. was more sedated) versus the control group, as well as lower metanephrine and normetanephrine/creatinine ratios at all but one time interval, in addition to fewer desaturation events. There were no differences in ventilatory requirements or in short term outcomes, including: severity of RDS, PDA, air leak, BPD, IVH, PVL, days of mechanical ventilation and oxygen therapy, growth, hospital stay and enteral feeding.

Not only is this study quite small, but it is also unclear how the nurse could be blinded to the treatment group if the control group received no infusion. In addition, the authors did not consider the number of painful procedures for each infant. It would have been interesting to use other tools such as PIPPS and NIPS in addition to the behavioral sedation scoring. The importance of this study, however, is that it suggests that fentanyl has continuously sedating effects at routine doses and may reduce stress in preterm infants.

Lago P, Benini F, Agosta C, Zacchello F. Randomised controlled trial of low dose fentanyl infusion in preterm infants with hyaline membrane disease. *Arch Dis Child Fetal Neonatal Ed*. 1998; 79: F194-F197.

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LONG-TERM OUTCOMES: OVERALL MORBIDITY

Hu S, Sheng WS, Lokensgard JR, Peterson PK. Morphine induces apoptosis of human

microglia and neurons. *Neuropharmacology*. 2002;42: 829-836.

MacGregor R, Evans D, Sugden D, Gaussen T, Levene M. Outcome at 5-6 years of prematurely born children who received morphine as neonate. *Arch Dis Child Fetal Neonatal Ed*. 1998;79: F40-F43.

In vitro and follow up investigations into the effects of morphine on neurological development.

Hu et al conducted a controlled study to determine the effect of morphine on inducing apoptosis in human fetal microglial (M), astrocyte (A) and neuronal (N) cell cultures. M, A and N cells were obtained from 16-22 week aborted human fetuses. Cultures of each cell type were exposed to one of two doses of morphine or no morphine. After 5 days of culture, the morphine M and N cultures had 4 times as many apoptotic cells versus controls. Morphine A cultures showed no difference in apoptotic cell numbers versus controls. Histone-associated DNA fragments, indicators of apoptosis, were quantified for increasing concentrations of morphine. N and M cells had increased amounts of these fragments which correlated with increasing concentrations of morphine. Apoptosis occurred earlier in N cultures versus M cultures. Naloxone blocked morphine's apoptotic effect by >55% in N and M cultures. Using a caspase-3 inhibitor, the authors showed that, in the presence of morphine, the inhibitor diminished apoptosis in both N and M cultures. The A cultures were not susceptible to morphine-induced apoptosis in any of the experiments.

The authors have shown that morphine, likely via an opioid receptor, induces apoptosis in N and M cells via the caspase-3 pathway. Astrocytes do not appear susceptible to this morphine-opioid receptor-caspase-3 apoptosis pathway. The cell cultures are from early second trimester fetuses. Thus, these findings may be important clinically for fetuses exposed to opiates during that period of development. The findings cannot be generalized to infants at later gestational ages.

To investigate long-term outcomes, MacGregor et al enrolled 57 of the survivors of 2 studies which had exposed ventilated infants born <34 weeks to morphine. The infants included from the first study received 50-100g/kg/hr of morphine for a median time of 5 days. In the second study, the infants received a 100 μ g/kg loading dose followed by 25g/kg/hr of morphine for a median time of 56 hours. The control group (N=33) was composed of infants from either study who had received pancuronium or placebo. At age 5-6 years, the children were evaluated by the Weschler Preschool and Primary Scale of Intelligence (WPPSI-R), the Movement Assessment Battery for Children and the Child Behaviour Checklist. Thirty-nine children had their TSH levels measured.

The death and disability outcomes for the children from the initial studies, regardless of treatment, were similar, in that there were no significant differences between the groups for WPPSI-R scores, motor impairment or behavioral problems. The authors conclude that morphine does not adversely affect IQ, motor function or behavior at ages 5-6 years. TSH values for both the control and morphine groups were normal.

Note, however, that this study is small, and further, that the children in the control group were not the same between the two studies. In addition, different morphine doses were given for short intervals and for different lengths of time in the two studies. It would be more helpful to look at the effects of longer term chronic opiate exposure on outcomes in a properly controlled trial. Despite these flaws, the authors have attempted to obtain crucial data on outcomes after opiate exposure.

Hu S, Sheng WS, Lokensgard JR, Peterson PK. Morphine induces apoptosis of human microglia and neurons. *Neuropharmacology*. 2002;42: 829-836.

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LONG-TERM OUTCOMES: PAIN THRESHOLDS

Buskila D, Neumann L, Zmora E, Feldman M, Bolotin A, Press J. Pain sensitivity in prematurely born adolescents. Arch Pediatr Adolesc Med. 2003;157: 1079-1082.

Grunau R, Weinberg J, Whitfield MF. Neonatal procedural pain and preterm infant cortisol response to novelty at 8 months. Pediatrics. 2004;114:e77-e84.

Bhutta AT, Rovnaghi C, Simpson PM, Gossett JM, Scalzo FM, Anand KJS. Interactions of inflammatory pain and morphine in infant rats: Long-term behavioral effects. Physiol Behav. 2001;73: 51-58

Three studies investigate long-term pain sensitivity in pre-terms.

Buskilla et al performed a case-control study to evaluate the tenderness thresholds in preterm adolescents by tender-point count and dolorimetry. Sixty adolescents with birth weights <1500g and gestational age <35 weeks and 60 peers born at full-term were enrolled. The authors manually assessed each teen at 18 tender points to determine tenderness or no tenderness. These points are used in rheumatological studies to assess nonarticular tenderness. A dolorimeter, a device which gradually applies increasing pressure to a point via a footplate, was used for 9 tender-point sites and 4 control sites. The participants completed visual analog scales (VAS) to evaluate pain, fatigue, morning stiffness and anxiety.

The adolescents born prematurely had tenderness at a higher number of tender points and had lower tenderness thresholds on dolorimetry. Females had more tender points and lower tenderness thresholds versus males in both the preterm and term groups. VAS scores were not different between the groups except for a small number of reports of fatigue and anxiety in the preterm group. Mechanical ventilation and length of stay were not correlated with tenderness.

The case-controlled study performed by Grunau and colleagues assessed cortisol levels in 8 month old corrected chronological age former pre-term infants at baseline, after novel toy introduction (post 1), and again after developmental assessment (post 2). Pre-term infants were divided into ≤ 28 weeks (N=19) and 29-32 weeks (N=34) gestation groups. Control infants (N=22) were born at term. The authors obtained salivary cortisol levels pre-intervention, after introducing novel toys, and again after performing Bayley scales and the Movement Assessment of Infants. Hospital charts were reviewed for number of skin-breaking procedures, illness severity, mechanical ventilation, medications, birth weight and gestational age.

The authors report higher basal and post 1 levels of salivary cortisol in the ≤ 28 week group. The 29-32 week group's post 1 cortisol level decreased from basal. Having more skin-breaking procedures as a neonate predicted higher basal and post 1 cortisol levels. The amount of opiate exposure did not correlate with cortisol levels. Gestational age was not correlated with basal cortisol levels. The authors postulate that the exposure to pain disrupts the development of the hypothalamic-pituitary-adrenal axis, and this disruption is not modified by morphine exposure.

Bhutta et al's controlled trial assessed the effects of chronic inflammatory pain during the neonatal period on pain thresholds, body weight, ethanol preference and locomotor activity in adult rats. There are four experimental groups which received interventions on post-natal days 1-7: controls (C = no intervention), the pain only (IP = daily formalin injections into the forepaws), morphine only (M = daily dose) and pain plus morphine (IP+M = morphine prior to formalin injections). The authors measured pain thresholds by hot plate (HP) and tail-flick (TF) tests, ethanol preference, locomotor activity and body weight at adult ages.

IP males and females and IP+M females exhibited increased HP latencies, i.e. had higher pain thresholds, versus C. Morphine decreased this effect in males. TF latencies were the same for all female groups and shorter than those for males. M males had longer TF latencies versus C. Ethanol preference was decreased versus C for the IP and M groups. Baseline locomotor activity was decreased in IP males. IP+M males and females and IP males had decreased adult body weights versus C.

This study demonstrates that exposure to either pain or morphine in the neonatal period can alter pain thresholds and behavioral responses. When morphine is used for treatment of pain, the effect is not additive, rather, morphine treatment ameliorated some of the long term effects, especially in the male animals.

Buskila D, Neumann L, Zmora E, Feldman M, Bolotin A, Press J. Pain sensitivity in prematurely born adolescents. *Arch Pediatr Adolesc Med.* 2003;157: 1079-1082.

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Bhutta AT, Rovnaghi C, Simpson PM, Gossett JM, Scalzo FM, Anand KJS. Interactions of inflammatory pain and morphine in infant rats: Long-term behavioral effects. *Physiol Behav.* 2001;73: 51-58

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Credit Designations [back to top](#)

Physicians

The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 0.5 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Nurses

The Institute for Johns Hopkins Nursing designates this activity for a maximum of 0.5 contact hours for this eNewsletter.

Respiratory Therapists

Contact your state licensing board to confirm that AMA PRA category 1 credits are accepted toward fulfillment of RT requirements.

Target Audience [back to top](#)

This activity has been developed for Neonatologists, NICU Nurses and Respiratory Therapists working with Neonatal patients. There are no fees or prerequisites for this activity.

Learning Objectives [back to top](#)

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CE activity. At the conclusion of this activity, participants should be able to:

- Evaluate the information presented to develop a more complete understanding of the issues surrounding the recognition of neonate pain, analgesia options suitable for neonates, and the potential long-term outcomes of the various treatment modalities discussed.
- Demonstrate a more complete understanding of the advantages/disadvantages of sucrose and opiates as analgesic agents.
- Use the information presented herein as a basis for decision making in providing safe and maximally effective analgesia for neonates in your clinical practice.

Faculty Disclosure Policy Affecting CE Activities [back to top](#)

As providers accredited by the Accreditation Council for Continuing Medical Education and American Nursing Credentialing Center, it is the policy of The Johns Hopkins University School of Medicine and The Institute of Johns Hopkins Nursing to require the disclosure of the existence of any significant financial interest or any other relationship a faculty member or a provider has with the manufacturer(s) of any commercial product(s) discussed an education presentation. The presenting faculty reported the following:

- Dr. Nogee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

Unlabelled/Unapproved Uses [back to top](#)

In accordance with the ACCME and ANCC Standards for Commercial Support, the audience is advised that one or more presentations in this continuing education activity may contain reference(s) to unlabeled or unapproved uses of drugs or devices.

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