Pain Management, Morphine Administration, and Outcomes in Preterm Infants: A Review of the Literature

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Abstract

Infants in the Neonatal Intensive Care Unit may experience a myriad of painful procedures and stressful experiences. Pain management for infants requiring mechanical ventilation is complex and challenging especially in the preterm population. Many infants may not receive analgesia, primarily due to the unknown long-term neurodevelopmental effects of morphine exposure on the developing brain. Currently, there is no consensus on how to treat pain related to mechanical ventilation due to conflicting scientific evidence lacks clarity and certainty about the role of morphine in pain in preterm infants. The Advance Practice Neonatal Nurse must make the best use of available information about morphine analgesia for the preterm infant, and use it to guide policy and practice for infants. The Advance Practice Neonatal Nurse must use his/her clinical expertise to judicially balance the risks and benefits of morphine analgesia, when used, and tailor the treatment plan to each infant's specific needs.

Infants in the neonatal intensive care unit (NICU) may experience a myriad of painful procedures and stressful experiences.[1,2] There is evidence and increasing awareness that infants, including preterm infants, are capable of experiencing pain.[1–4] Preterm infants especially are often subjected to repetitive or prolonged pain stimuli related to the use of mechanical ventilation to support their pulmonary immaturity.[5,6]

Pain management for infants requiring mechanical ventilation is complex and challenging.[7] Infants may not receive analgesia as a result of inconsistent interpretation of pain cues, or concerns about variable pharmacokinetics of analgesics, such as morphine sulfate (MS) and the unknown long-term neurodevelopmental effects of MS exposure on the developing brain.[8,9] To further compound the problem of assessing pain and response to analgesics such as MS, there are no pain tools that measure prolonged pain specifically in preterm infants.[10] Recent literature suggests that pain may be processed cortically without eliciting a behavioral reaction in both preterm and term infants.[11] Preterm infants may display diminished pain responses compared with term infants, making pain assessment even more difficult to evaluate.[12] Although the presence of painful stimuli is often apparent, the absence of behavioral response by the preterm infant may result in underestimation and inadequate management of pain in this unique population.

Adverse Consequences of Pain

Fetal brain growth is rapid in the third trimester, making preterm infants exposed to early pain extremely vulnerable to neurologic insults during this critical window of development.[5,13,14] Normal neurodevelopment relies on intrauterine neuroprotection, and extrauterine noxious stimuli eliciting pain may modify expected neuronal cell proliferation, migration, and differentiation.[15] Pain responses in infants across various gestational age (GA) include diaphragmatic splinting, crying, tachycardia, and hypertension secondary to sympathetic activation.[16] These responses to pain may cause fluctuations in intracranial pressure and cerebral blood volume, increasing the risk of complications such as intraventricular hemorrhage (IVH).[17] There is growing evidence that repeated pain experiences in infancy can impact long-term

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This article is not intended to be a comprehensive review of every state's law, nor is it intended to provide legal advice. Seek legal counsel in the event you have questions regarding legal issues.

Accepted for publication May 2011.

http://dx.doi.org/10.1891/0730-0832.31.1.21

psychosocial development seen as neurobehavioral disorders and cognitive deficits in childhood and adolescence.[9,14,15]

MORPHINE PHARMACOLOGY

Morphine is a naturally occurring opioid most commonly used in the NICU for analgesia.[18–20] Morphine is an agonist at the mu and kappa receptors and also binds to delta receptors in the spinal cord and brain.[20,21] The liver metabolizes MS into *morphine-3-glucuronide* (M3G), an opioid antagonist and *morphine-6-glucuronide* (M6G), a powerful analgesic more potent than MS.[19,21,22] In preterm infants, there is a decreased production of M6G and increased production of M3G because of reduced glucoronidation.[23] It has been proposed that the M3G to M6G ratio may be responsible for the decreased analgesic effect of MS in preterm infants.[22,23] Because of the unique MS pharmacokinetics in preterm infants, MS dosing administration to attain adequate analgesia remains a challenge.

Because of conflicting scientific evidence, some of which suggests that MS may increase the incidence of poor health outcomes, there is no consensus on how to treat procedural pain, including pain related to mechanical ventilation in preterm infants.[18,24] One approach is the use of preemptive continuous MS infusion based on the assumption that mechanical ventilation is painful; the other is treating pain on an as-needed basis using intermittent bolus administration of MS.[7] Therefore, this literature review will examine neurologic, cardiovascular, and pulmonary outcomes associated with the use of continuous MS infusions and intermittent bolus administration of MS in infants.

A literature search was performed using the following databases for the years 1999–2011: PubMed, Ovid, MEDLINE, ScienceDirect, Blackwell Synergy, and Google Scholar using combinations of the following search terms: MS, opioid, analgesia, pain, mechanical ventilation, preterm, infant, neonate, IVH, periventricular leukomalacia (PVL), and NICU. Studies were included if they examined the use of continuous MS infusion and/or intermittent bolus administration of MS (referred to as *additional intermittent analgesia* in some investigations) in mechanically ventilated infants and measured outcomes including pain, neurologic, cardiovascular, and pulmonary health outcomes. Six investigations were selected meeting the aforementioned criteria, which included a pilot trial and five randomized controlled trials (RCTs). While Cochrane Reviews recently published a systematic review in ventilated infants receiving opioids,[24] this manuscript focuses specifically on MS and also highlights nursing implications for the NICU nurse and the advance practice neonatal nurse (APNN), which distinguishes this review from others.

LITERATURE REVIEW

Pain and stress may play a role in negative neurologic outcomes in preterm infants. Anand and colleagues proposed that negative neurologic outcomes in preterm infants may be reduced by prophylactic use of analgesia or sedation.[16] In their Neonatal Outcomes and Prolonged Analgesia in Neonates (NOPAIN) trial, the investigators designed a pilot investigation to define the incidence of select clinical outcomes in a preterm population, to estimate the effect size, and to calculate the sample size needed for a larger clinical trial. Primary dependent variables included the incidence of poor neurologic outcomes, defined as *neonatal death* or severe IVH or PVL. Infants were stratified by GA (24–26, 27–29, and 30–33 weeks) and randomized to receive continuous infusions of MS (analgesia), midazolam (sedation), or placebo (Table 1). All infants were eligible to receive MS labeled for additional analgesia if the infant was determined to be in pain. The COMFORT tool was used to assess sedation, whereas the premature infant pain profile (PIPP)[26] was used to assess pain.[25,26] Table 2 provides a summary of these and other pain tools.

There were no significant differences in the demographic and clinical variables for infants in the NOPAIN trial that may have influenced outcomes. Poor neurologic outcomes occurred in 24 percent of infants in the placebo group, 32 percent in the midazolam group, and 4 percent in infants in the MS group ($\chi^2 = 7.04$; $p<.03$). The MS group was the only group that had significantly reduced PIPP scores from baseline ($p<.002$), reflecting adequate analgesia. The use of additional analgesia was quantified, but no significant differences were found between the groups, which may have contributed to the fact that no significant differences were found for pulmonary or neurobehavioral outcomes between the groups.

Anand and colleagues demonstrated benefits of analgesia and sedation in preterm infants who required ventilatory support and suggested that preemptive MS analgesia may improve neurologic outcomes.[16] Although small, this was an important pilot for determination of appropriate analgesia in preterm infants. There were some weaknesses to this pilot study, however. Although infants in the MS group had fewer poor neurologic outcomes compared with midazolam and placebo, results from the small sample cannot be generalized to all preterm infants. Maternal demographics and antenatal conditions were similar in all groups, but it is unclear to what extent MS or other variables such as hospital course related to severity of illness affected neurologic outcomes as evidenced by significantly different Neurodevelopmental Assessment of the Preterm Infant (NAPI) scores ($p<.01$) despite similar Clinical Risk Index for Babies (CRIB) scores between all three groups. The lack of standardization of cranial ultrasonography may have led to variation in interpretation of the severity of IVH reported, despite use of similar criteria for diagnosis and grading of IVH. The results from this pilot study provided support for a large, multicenter trial.

Following the NOPAIN pilot study, Anand and colleagues conducted the Neurologic Outcomes and Preemptive Analgesia in Neonates (NEOPAIN) trial to investigate whether preemptive administration of MS analgesia would decrease early neurologic injury in ventilated preterm infants.[27] Primary dependent variables were neonatal death, severe IVH, PVL, or a composite outcome of these variables. This double-blind RCT included 898 preterm

TABLE 1 ■ Characteristics of Included Investigations

Study	Subjects	Intervention Comparison Group	Treatment Schedule Additional Analgesia	Outcomes (Short-Term Neurologic, Pulmonary, or Cardiovascular)
Anand et al., 1999	67 infants 24–32 weeks GA, postnatal age ≤72 h, ventilated for <8 h MS (n = 24) Midazolam (n = 22) Placebo (n = 21)	MS loading dose 100 mcg/kg MS infusions based in GA: 10, 20, and 30 mcg/kg/h for 23–26, 27–29, and 30–32 weeks GA respectively Midazolam loading dose 200 mcg/kg Midazolam infusions based in GA: 20, 40, and 60 mcg/kg/h for 24–26, 27–29, and 30–32 weeks GA respectively Placebo group received an infusion of dextrose 10% in water.	Study drug continued as clinically necessary for up to 14 days. Drug weaned per protocol. Additional analgesia with MS allowed in all three groups if infant determined to be in pain.	Poor neurologic outcomes in 24% placebo group, 32% midazolam group, and 4% morphine group (χ^2 = 7.04; p<.03). MS group had significantly higher COMFORT scores 12 hours after the infusion was stopped, (p<.005). PIPP scores were significantly reduced in the MS (p<.001) and midazolam (p<.002) groups compared with placebo, reflecting adequate analgesia. No significant differences in additional analgesia are given to infants in any group (p>.80, all days). No significant differences between three groups for ventilator days, CPAP or oxygen therapy, and neurobehavioral outcomes of the infants at 36 weeks' PCA.
Anand et al., 2004	898 infants, 23–32 weeks GA, intubated within 72 h postnatal, ventilated for <8 h MS (n = 449) Placebo (n = 449)	MS loading dose 100 mcg/kg. MS infusions based in GA: 10, 20, and 30 mcg/kg/h for 23–26, 27–29, and 30–32 weeks GA respectively Placebo group received an infusion of dextrose 5% in water.	Study drug continued as clinically necessary for up to 14 days. Drug weaned per protocol. Additional analgesia with open label MS allowed in both groups if infant determined to be in pain.	No significant differences in severe IVH (p>.3493) or PVL (p>.2533) between the groups, however, the incidence of severe IVH was higher in the MS 27–29 week subgroup (p<.0429), as compared to the respective placebo subgroup. Severe IVH was related to younger GA (p<.0001), higher CRIB score (p<.0221), lack of antenatal steroids (p<.0001), maternal race (p<.0363), but not to treatment group (p>.2153). PVL was related to maternal chorioamnionitis (p<.0339), but not to GA (p>.9137) or to treatment group (p>.4080). Hypotension occurred more frequently in the MS group prior to the study infusion (p>.1672), following the loading dose (p<.0085), and after 24 hours of infusion (p<.0006). MS group remained ventilated longer (p<.0338). MS groups had significantly lower PIPP scores across all GAs at the 24-hour point of the study infusion (p<.0034). Placebo group received additional analgesia more frequently than the MS group (p<.0054). A higher incidence of severe IVH (p<.0209) was observed in the MS group than in the placebo group in infants who did not receive any additional analgesia.
Bhandari et al., 2005	898 infants, 23–32 weeks GA, intubated within 72 h postnatal, ventilated for <8 h MS (n = 449) Placebo (n = 449)	MS loading dose 100 mcg/kg. MS infusions based in GA: 10, 20, and 30 mcg/kg/h for 23–26, 27–29, and 30–32 weeks GA, respectively Placebo group received an infusion of dextrose 5% in water.	Study drug continued as clinically necessary for up to 14 days. Drug weaned per protocol. Additional analgesia with open label MS allowed in both groups if infant determined to be in pain Use of midazolam and other sedative or analgesic drugs was not allowed.	RDS (p>.29) and CRIB scores (p>.50) were comparable between the MS and placebo. MS group were ventilated significantly longer than the placebo group (p<.01). No significant differences between the MS and placebo in the incidence of air leaks or BPD No significant differences observed in the total days of ventilation (p>.94), duration of oxygen (p>.69), incidence of air leaks (p>.87), or BPD (p>.98) in the 23–26 weeks GA. MS infants had more ventilator days than placebo (p<.01), but days in oxygen was not significantly different (p>.95) in the 27–29 week GA. MS infants were ventilated significantly longer than placebo (p<.02) with no differences in oxygen days (p>.25) in the 30–32 weeks GA. MS group required significantly longer mechanical ventilation than the placebo group (p<.01).

(*continued*)

TABLE 1 ■ Characteristics of Included Investigations *(continued)*

Study	Subjects	Intervention Comparison Group	Treatment Schedule Additional Analgesia	Outcomes (Short-Term Neurologic, Pulmonary, or Cardiovascular)
Simons et al, 2003	150 infants admitted to NICU, postnatal age <3days, ventilated for <8 h MS (n = 73) Placebo (n = 77)	MS loading dose of 100 mcg/kg of MS followed by a 10 mcg/kg/h. (All infants of various GA received the same dose/kg) Placebo group infants received dextrose 5% in water.	Study drug continued as clinically necessary for up to 7 days. Any infant determined to be in pain received an additional dose of 50 mcg/kg followed by 5–10 mcg/kg/h open-label MS infusion	No significant differences in pain scores among the groups with suctioning (PIPP, p>.94; NIPS, p>.58; VAS, p>.14). Pain scores after the MS loading dose did not differ significantly among the groups (VAS, p>.46; NIPS, p>.47). The pain scores were higher when MS was not administered before intubation (VAS, p<.06; NIPS, p<.02). No significant differences in the pain scores among the treatment groups (PIPP, p>.94; NIPS, p>.58; VAS, p>.14) or with the use of additional analgesia (PIPP, p>.48; NIPS, p>.83; VAS, p>.59) MS infusion (p>.63) and additional analgesia (p>.73) use were not associated with increased incidence of severe IVH, PVL, or death within 28 days. IVH was significantly higher in the placebo group as compared with the MS group (p<.04). Significantly, more infants in the placebo group received additional analgesia compared to the MS group (p>.10).
Simons et al., 2006	150 infants admitted to NICU, postnatal age <3days, ventilated for <8 h MS (n = 73) Placebo (n = 77)	MS loading dose 100 mcg/kg of followed by a 10 mcg/kg/h. (All infants of various GA received the same dose/kg) Placebo group infants received dextrose 5% in water.	Study drug continued as clinically necessary for up to 7 days. Any infant determined to be in pain received an additional dose of 50 mcg/kg followed by 5–10 mcg/kg/h open-label MS infusion	No significant differences between the two groups in the treatment of hypotension (p>.87). MS group were significantly more likely to have demonstrated transient hypotensive events than the placebo group (p<.004), however, the median MAP did not differ among the groups (p>.88). Seventy percent of infants who received additional analgesia in the placebo group experienced hypotension, whereas 38% who did not receive additional analgesia also became hypotensive (p<.018). In the MS group, 80% of infants who received additional analgesia became hypotensive and 68% who did not receive additional analgesia also became hypotensive (p>.53). No significant differences in the variability of MAP among the MS and the placebo groups (p>.81). No significant differences in variability in MAP associated with the amount of additional analgesia (p>.80) or the GA (p>.30). No significant differences in BP between infants with IVH and those without IVH (p>.14).
Carbajal et al.,2005	42 infants, 23–32 weeks GA, intubated within 72h postnatal, ventilated for <8 h MS (n = 21) Placebo (n = 21)	MS loading dose 100 mcg/kg. MS infusions based in GA: 10, 20 and 30 mcg kg/h for 23–26, 27–29 and 30–32 weeks GA respectively. Placebo group received an infusion of dextrose 5% in water.	Study drug continued as clinically necessary for up to 14 days. Drug weaned per protocol. Additional analgesia with open-label MS allowed in both groups if infant determined to be in pain	No significant differences in mean DAN scores at T1, T2, and T3 between the two groups. There were no significant differences in mean PIPP scores at T1, T2, and T3 between the two groups. The DAN scores at T1, T2, and T3 were not statistically different over time and the interaction between this and treatment groups were not statistically significant. However, PIPP scores at T1, T2, and T3 were statistically different over time (p<.044), but the interaction between this factor and groups was not statistically significant (p>.860). There were no significant differences in mean plasma MS levels between the placebo (0.44 ± 1.79 ng/mL) and MS group (63.36 ± 33.35 ng/mL) and there was no correlation between plasma MS and pain scores at T3 (DAN, R = −0.05, p>.16; PIPP, R = −0.02, p>.58).

Key: GA = gestational age; MS = morphine sulfate; COMFORT; PIPP = premature infant pain profile ; CPAP = continuous positive airway pressure ; PCA = patient controlled analgesia ; IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia ; CRIB = clinical risk index for babies; RDS = respiratory distress syndrome ; BPD = bronchopulmonary dysplacia ; MAP = mean arterial pressure; DAN = Douleur Aiguë Nouveau-né.

TABLE 2 ■ Pain Tools

Pain Tool	Description
COMFORT[25]	The COMFORT tool was developed to assess distress using eight physiologic and behavioral variables including mean arterial pressure, HR, RR, muscle tone, facial tension, alertness, calmness/agitation, and physical movement.
Douleur Aiguë Nouveau-né scale[39]	The DAN scale is a behavioral scale developed to rate acute pain in term and preterm infants with scores ranging from 0 (no pain) to 10 (maximal pain), based facial expressions, limb movements, and vocal expression. The DAN scale was found to be sensitive and specific for pain scores of 3 for 95% of painful procedures and 2 for 88% of sham procedures. There was good internal consistency (coefficient = .88) and good interrater agreement (r = 91.2).
Neonatal Infant Pain Scale[33]	The NIPS assesses acute procedural pain in preterm and term neonates by facial expression, cry, breathing patterns, arms, legs, and state of arousal, and has high interrater reliability (r = 0.92 − 0.97) and internal consistency (0.95, 0.87, and 0.88 for before, during, and after the procedure, respectively).
Premature Infant Pain Profile[26]	The PIPP score represents a composite score reflecting GA, behavioral state, HR, oxygen saturation, brow bulge, eye squeeze, and nasolabial furrow with construct validity (p<.0001), with interrater reliability coefficients of 0.93 to 0.96.
Visual Analogue Scale[32]	The VAS is a linear scale with no pain (0) to extreme pain (10) with good validity in estimating pain in the pediatric population.

infants <32 weeks gestation from 12 American and four European NICUs. Infants were stratified into three groups by GA and were randomized to either MS (n = 449) or placebo (n = 449) groups. Those in the MS group received a loading dose of MS followed by a continuous infusion based on GA (see Table 1). Both the MS and the placebo groups could receive additional open-label MS if determined to be in pain determined by PIPP pain scores.

Cranial ultrasonography determined the presence of IVH and/or PVL at 4 to 7 days of age and at 28–35 days for neonates born <30 weeks gestation or at 14–28 days for those born >30 weeks gestation in both groups. The CRIB score was used to assess the severity of illness in the infants.[28] Data on 446 MS infants and 444 placebo infants were analyzed. There were no differences in clinical and demographic characteristics between the groups, except for a greater use of antenatal magnesium in the placebo group.

Results of the study showed no significant differences in severe IVH, PVL, death, or composite outcome of the three previous outcomes between the combined GA groups; however, the incidence of severe IVH was higher in the MS 27–29 week subgroup (p<.0429) as compared with the respective placebo subgroup. For factors associated with primary outcomes, logistic regression showed that GA (p<.0001) and CRIB score (p<.0001) were significantly associated to composite outcome and neonatal death. The use of antenatal steroids (p<.0001) and GA (p<.0001) were significantly associated with severe IVH. Hypotension was observed more frequently in the MS group across combined GA groups throughout the study period, including prior to the MS infusion, which may have been a reflection of hemodynamic instability. When the use of additional analgesia was quantified, the placebo group infants received more frequent boluses than the MS group (p<.0054). A higher incidence of severe IVH (p<.0209) was observed in the MS group than in the placebo group in infants who did not receive any additional analgesia.

The investigators concluded that preemptive MS infusion in preterm infants requiring mechanical ventilation did not decrease the risk of severe IVH or PVL. The investigators reported that the increased rate of severe IVH in the 27–29 week MS subgroup may be secondary to higher MS infusion rates or decreased MS clearance in already hypotensive infants. However, authors acknowledge that further research is needed on factors affecting morphine pharmacokinetics in preterm infants to explain worse outcomes in the 27–29 week MS subgroup. It was also hypothesized that these infants may have received MS doses higher than 10 mcg/kg/h because use of additional analgesia was associated with severe IVH and PVL in both groups. There was great variability in the administration of additional analgesia among the NICUs, which may have influenced the outcomes.

One weakness of the study was not performing cranial ultrasonography prior to study infusions to assess baseline status in both groups. The investigators speculated that infants who received additional analgesia might have already developed a neurologic insult predisposing them to behaviors, which may have been misinterpreted as pain. Another weakness was the use of incrementally increasing dose/kg MS dosages for the three GA subgroups. Despite improved metabolism with increasing GA, the lack of standardization of MS dose may have affected pain and altered cardiovascular and neurologic outcomes. Strengthening this investigation was the large sample size, although the investigators fell short of their desired group size of 470 to support sufficient power for analyses and interpretation of results. However, despite the large sample size, the enrollment of preterm infants between 23 and

32 weeks GA with varying acuities from a variety of American and European NICUs with potentially different treatment practices limits the generalizability of these findings.

Bhandari and colleagues examined pulmonary outcomes using a cohort derived from the NEOPAIN trial,[29] including infants 23–32 weeks gestation, divided into three GA subgroups.[27] The investigators examined whether mechanically ventilated preterm infants who received preemptive MS would have improved pulmonary outcomes compared with those who received a placebo. Pulmonary outcomes included the number of ventilator, continuous positive airway pressure (CPAP) or oxygen therapy days, air leaks, and bronchopulmonary dysplasia (BPD). Infants in the MS (n = 449) group received a loading dose of MS followed by a continuous infusion based on GA (see Table 1). Placebo infants (n = 449) received D_5W as an infusion and both groups could receive additional open-label MS if determined to be in pain assessed using the PIPP (see Table 2).[26]

Despite similar incidence of respiratory distress syndrome (RDS) and CRIB scores in both groups, the infants in the MS group were ventilated significantly longer than the placebo group ($p<.01$). Overall, there was no increased incidence of adverse pulmonary events such as air leaks or BPD observed in the MS group compared with the placebo group. The MS group required significantly longer mechanical ventilation than the placebo group ($p<.01$), and upon closer examination, particularly infants in the 27–29 ($p<.01$) and 30–32 weeks ($p<.02$) were affected by the MS infusion.

Bhandari and colleagues concluded that because the MS and the placebo groups had similar acuity, differences in pulmonary outcomes were likely caused by the treatment effect of preemptive MS infusions.[29] The trend was for younger, smaller, and sicker infants to have received additional analgesia, and investigators speculated that these same infants with worse pulmonary outcomes were most likely to have been subjected to procedures managed with additional analgesia. After adjusting for infant characteristics such as birth weight (BW), CRIB scores, maternal chorioamnionitis, RDS requiring surfactant, and patent ductus arteriosus, infants who received preemptive MS did not differ from placebo in ventilator or CPAP dependent days, need for oxygen therapy, or incidence of air leaks and BPD.

The use of additional analgesia emerged as a powerful predictor for poor respiratory outcomes. In the placebo group, those infants who received additional analgesia were 3.4 times more likely to have pulmonary air leaks ($p<.01$), require an additional 2.6 days on high-frequency ventilation (HFV) ($p<.01$) and 3.2 days on CPAP ($p<.02$), and an additional 7.2 days on oxygen therapy ($p<.01$). In the MS group, those infants who received additional analgesia were 4.3 times more likely to have air leaks ($p<.01$), require an additional 6.7 days on positive-pressure ventilation ($p<.01$), conventional ventilation ($p<.04$), and HFV ($p<.01$). Days on CPAP were also increased by 2.9 days ($p<.04$) as well as an additional 8.1 days ($p<.01$) on supplemental oxygen in the MS group. The investigators concluded that the use of additional analgesia may have contributed to worse pulmonary outcomes and urge caution when using intermittent MS bolus to treat pain.

One limitation of this study was the failure to correlate the frequency of additional analgesia with respiratory outcomes. Morphine is a known respiratory depressant, therefore it is not surprising that those infants who received additional MS experienced an increased need for respiratory support.[30] Risk for respiratory depression should be anticipated when contrasting pharmocodynamics of MS in a 23-week GA versus a 32-week GA infant who can metabolize MS more effectively, despite using incremental MS dosing strategy based on GA.[19] Quantifying use of additional analgesia can help determine whether the infant's GA and comorbidities versus MS use alone contributes to poor pulmonary outcomes.

Strengths of this investigation included the large sample population and appropriate stratification of GA groups. In addition, this investigation examined multiple ventilatory variables known to contribute to BPD.[31] However, the study did not examine other BPD risks such as infection related to the duration of ventilation between the two groups. Evaluation of the use of additional analgesia allowed for identification of this as a predictor of worse pulmonary outcomes. Therefore, the use of intermittent MS in preterm ventilated infants must be used cautiously. This investigation was weakened by the wide range of GAs, which likely represented differences in pulmonary maturity and which may have contributed to the significant different ventilatory outcomes. Greater dose/kg of MS may have contributed to the significant difference in ventilatory outcomes, despite no difference in the incidence of BPD. This highlights the complexity of BPD development and lack of clarity in implicating MS as a cause.

Simons and coworkers implemented a double-blind RCT to investigate the effects of MS in relation to the incidence of IVH and poor neurologic outcomes, defined as severe IVH, PVL, or death within the first 28 days of life.[4] The investigators tested whether preemptive MS would improve neurologic outcomes and reduce pain responses to stimuli, including mechanical ventilation and ET suctioning. MS group infants received a loading dose of 100 mcg/kg of MS followed by a 10 mcg/kg/h continuous infusion whereas placebo group infants received D_5W (see Table 1). Any infant determined to be in pain received an additional dose of 50 mcg/kg followed by 5–10 mcg/kg/h open-label MS infusion. All preterm and term infants admitted to one of two level III NICUs in the Netherlands and who required mechanical ventilation were eligible for inclusion; those with major congenital or facial anomalies, severe asphyxia, severe IVH, neurologic disorders, or exposure to any neuromuscular agents were excluded.

Seventy-three and 77 infants were randomly assigned to the MS group and to the placebo group respectively, and were stratified into groups by GA. Pain assessment tools included the Visual Analogue Scale, the Neonatal Infant Pain Scale, and the PIPP (see Table 2).[26,32,33] The infant's pain was assessed using the tools before the use of the MS or placebo

infusions 30 minutes after the loading dose and twice a day at predetermined times before and after ET suctioning.

Demographic characteristics, including GA, BW, and CRIB scores were similar in the groups. There were no significant differences in pain scores between the groups with suctioning, and pain scores after the MS loading dose did not differ significantly between the groups. VAS scores were higher in girls compared with boys ($p<.03$) and higher in Center 2 compared with Center 1 ($p<.02$). The pain scores were higher when MS was not administered before intubation (VAS $p<.06$; NIPS; $p<.02$). There were no significant differences in the pain scores between the treatment groups or with the use of additional analgesia.

Although younger GA ($p<.005$), higher CRIB scores ($p<.004$), and male gender ($p<.003$) were associated with an increased incidence of severe IVH, PVL, or death within 28 days, logistic regression analyses revealed that both MS infusion and additional analgesia use were not. Intraventricular hemorrhage was significantly higher in the placebo group as compared with the MS group ($p<.04$) and associated with younger GA ($p<.006$), small for GA infants ($p<.05$), and transport from another hospital ($p<.04$). Significantly, more infants in the placebo group received additional analgesia compared with the MS group ($p>.1$) with similar dosages of 4.3 and 3.0 mcg/kg/h in the placebo and the MS groups, respectively.

The investigators concluded that pain scores between treatment groups did not reflect positive analgesic effects of MS. The PIPP and NIPS used in this investigation have been validated for acute pain, but their validity in assessing prolonged pain associated with mechanical ventilation has not been documented.[26,33,34] Baseline and pain scores before the loading dose were low, indicating either minor pain, absence of pain, or infant inability to mount a measurable pain response. This investigation demonstrated that neurologic outcome improved in a small subset of preterm infants, and therefore the use of preemptive MS in this subset warrants further examination.

Strengths of this investigation were a double-blind design and the standardization of MS infusions across the GAs. The use of additional analgesia bolus followed by an additional infusion may have decreased serum fluctuations of MS delivering superior analgesia, compared with repeated bolus administrations. This study was weakened by the lack of standardized observations of pain between the two centers. Another weakness involved the use of both term and preterm infants in the same investigation. Morphine metabolism and clearance differ in term and preterm infants as does the permeability of the blood–brain barrier to morphine, which may have impacted the pain scores.[19] Finally, preterm infants have very different morbidity risks for IVH and other neurologic outcomes compared with term infants, thus limiting use of these variables may have strengthened this investigation.[13,35] Although the design of the investigation reflects realistic practices used in the NICU, its generalizability is limited to similar populations and centers.

Simons and associates conducted a secondary analysis of the data from the previously described randomized trial.[4,36] In this secondary data analysis, Simons and associates examined the effects of MS infusion on arterial blood pressure (BP) to test whether these infusions would be associated with an increased risk of hypotension and decreased BP variability.[36] The methods and sampling procedures were described in the previous study by Simons and coworkers.[4] (see Table 1).

There were no significant differences in baseline MAP or MAP values during the study between the MS and the placebo group. There were no significant differences observed between the two groups in the treatment of hypotension, suggesting that MS alone did not influence the likelihood of clinically significant hypotension. Taking into account the use of additional analgesia, significantly more infants in the placebo who received additional analgesia became hypotensive compared with the infants in the same group who did not receive additional analgesia ($p<.004$). In contrast, in the MS group, there was no significant difference in the number of hypotensive infants among those who received additional analgesia and those who did not. It is also possible that hypotension seen in the study period may not have reflected the effects of MS, but rather physiologic changes in BP that normally occur during the first 72 hours of life.[37]

There were no significant differences in BP or the incidence of hypotension in infants with and without IVH, and in addition, the incidence of IVH was not increased in infants with hypotension. In the original investigation, Simons coworkers. demonstrated a significantly lower incidence of IVH in the MS group; however, in this secondary analysis of data, no significant differences in BP between infants with IVH and those without IVH were observed.[4,36] In summary, MS infusion was not associated with hypotension and the relationship to the development of IVH could not be determined.

Carbajal and colleagues examined the analgesic efficacy of continuous MS infusion on heelstick-induced pain in preterm infants.[38] This investigation was nested in the NEOPAIN trial previously critiqued.[27] Of 121 eligible infants, 42 preterm infants 23–32 weeks gestation intubated before 72 hours of age and ventilated for <8 hours were enrolled. Equal number of infants ($n = 21$) were randomized to either the placebo or MS group according to methods described previously for the NEOPAIN trial (see Table 1).[27] Enrolled infants were expected to receive heelsticks for blood glucose determination as part of the standard of care. Primary dependent variables were pain responses to these three heelsticks, before (T1), two to three hours (T2), and 20–28 hours after the loading dose (T3). In addition, plasma MS levels were measured at T3. Complete data from 17 infants in the MS group and 14 from the placebo were analyzed.

Pain responses to heelsticks were assessed by an independent blinded observer using the Douleur Aiguë Nouveau-né (DAN) scale and the PIPP (see Table 2).[26,39] Infants in both groups had comparable demographic variables such as GA and BW. No significant differences were observed in either

the mean DAN or PIPP scores during all three heelsticks between the two groups. The DAN scores during the heelsticks were not statistically different over time and the interaction between this and treatment groups were not statistically significant. However, PIPP scores at T1, T2, and T3 within groups were statistically different over time ($p<.044$), but the interaction between this factor and groups was not statistically significant. There was no correlation found between plasma MS and pain scores during the last heelstick.

Carbajal et al. demonstrated that MS loading dose followed by a continuous infusion did not provide adequate analgesia for heelstick-induced pain among ventilated preterm infants.[38] The investigators proposed the lack of analgesic effects were related to immature opioid receptors or impaired MS metabolism by the immature liver leading to decreased M6G (potent analgesic) and increased M3G (MS and M6G antagonist) production. Decreased M6G in preterm infants may explain the lack of association between plasma MS levels and pain scores at T3.[40,41] Based on their data, the investigators question the efficacy of MS for acute pain from invasive procedures in preterm infants. Clinicians need to consider bolus administration of MS with caution for invasive procedures that may require pharmacologic intervention if the infant is receiving a continuous infusion of MS.

Strengths of this investigation included the use of two validated pain tools to assess pain during heelstick and the use of three consecutive sampling times. Additional strengths were the use of heelstick, a realistic type of pain stimulus often encountered in the preterm population and the use of an independent observer to assess these pain responses. Weakness included the smaller than intended sample size that affected the power of the study. It also appeared that the investigators broke protocol by not providing additional open-label MS in either group during the study period when adequate analgesia during heelsticks was not apparent. To further test the analgesic efficacy of MS, bolus dosage should be given prior to the procedure with subsequent pain response assessments. It appears from this study that MS infusion does not provide adequate analgesia for acute procedural pain in ventilated preterm infants.

DISCUSSION AND APPLICATION

The primary objective of this critical review of the literature was to examine select neurologic, cardiovascular, and pulmonary outcomes in infants associated with the use of continuous MS infusions and intermittent bolus administration of MS. Relief of pain was a goal of most investigations critiqued for this review. While pain scores were significantly lower in the MS group compared with placebo in the NOPAIN and NEOPAIN trials, Simons and coworkers and Carbajal and colleagues found that pain scores did not differ between treatment and placebo groups.[4,16,27,38] Based on these investigations, the analgesic effects of MS to relieve pain related to mechanical ventilation in preterm infants are unclear.[4,16,27] The different methodologies as well as pain assessment tools employed in individual investigations may explain these differences in outcomes between the investigations. For example, the pain assessment tools used in the investigations were not designed to assess prolonged pain related to mechanical ventilation of preterm infants and thus may not have accurately reflected this outcome. Anand and colleagues noted great variation in administration of additional analgesia among sites, highlighting the challenges of accurate pain assessment and management.[27] Pain responses from both preterm and term infants were included in the Simons trial.[4] However, often pain responses are diminished in preterm infants which may have influenced the pain score results.[12,42] The type of pain stimulus used by Carbajal and colleagues was more representative of acute pain and differed from that used by the other investigators.[38] Finally, the pain assessment tools used were not uniform across the literature critiqued, limiting the ability to accurately make an accurate comparison of pain responses. It is unknown whether current tools can accurately assess prolonged pain or the analgesic effect of MS in the preterm infant, and future research should examine this. It is also unclear whether MS has effective analgesic properties across various GAS, types of procedural pain, and modes of administration. There is a great need to further investigate MS pharmacokinetics and pharmacodynamics in relation to pain responses especially in the preterm population.

The use of additional analgesia bolus for breakthrough pain was not without risk, and worse neurologic and pulmonary outcomes were noted by two investigators.[27,29] The terms *additional analgesia* and *intermittent MS bolus* have been used interchangeably in this review. Although the use of additional analgesia in the placebo group appeared to be intermittent bolus administration, some infants in the MS group who received additional analgesia were exposed to both continuous and intermittent MS, which may have altered outcomes. Furthermore, additional analgesia used in the Simons and coworkers trial included an intermittent bolus followed by an additional continuous infusion.[4] Infusion rates were standardized in two investigations,[4,36] but incrementally increased by GA in others,[16,27,29] which may have affected pain assessment and outcomes. Future investigations should standardize both dosing and use of additional analgesia for breakthrough pain.

Prevention of adverse neurologic outcomes was a goal of several investigators but led to conflicting results. The NOPAIN small pilot study suggested that preemptive MS may improve poor neurologic outcomes;[16] however, the much larger randomized clinical NEOPAIN trial revealed that preemptive MS infusion did not decrease the frequency of severe IVH, PVL, or death.[27] In addition, there was an increased rate of severe IVH in infants who were 27–29 weeks gestation and additional analgesia was associated with an increased rate of severe IVH, PVL, or death.[27] Simons and coworkers found that preemptive MS infusions significantly reduced IVH but did not reduce the incidence of poor neurologic outcomes.[4]

Pulmonary and cardiovascular stability were measured as an outcome by several investigators. Anand et al. reported no

significant differences in pulmonary outcomes among groups, and Simons and coworkers also reported no significant difference in duration of mechanical ventilation.[4,16] In these cases with no significant difference in pulmonary outcomes, the total MS administered between groups was not significantly different. However, when differences in outcome occurred, it was most likely affected by the use of additional analgesia. Bhandari et al., while not finding that MS infusion improved short-term pulmonary outcome, reported that the infants in the MS group who received additional analgesia had the worst outcomes.[29] Anand and colleagues and Simons and associates reported hypotension as an indicator of cardiovascular outcome, but no relationship between continuous MS infusion and this variable was determined.[27,36]

IMPLICATIONS FOR THE NICU NURSE AND ADVANCED PRACTICE NEONATAL NURSE

The "Consensus Statement for the Prevention and Management of Pain in the Newborn" emphasizes that pain management is an essential part of health care delivery in all infants across various GA and severity of illness.[1] The American Academy of Pediatrics together with the Canadian Paediatric Society states that pain prevention in infants should be a priority for all caregivers.[43] Common therapeutic procedures such as mechanical ventilation and ET suctioning are considered painful, and management strategies including use of pharmacologic agents for analgesia should be strongly considered.[1] According to the literature critiqued, it is unclear which method of MS analgesia delivery is most effective, or whether minimizing pain with a preemptive approach using MS will improve short-term neurologic, cardiovascular, or pulmonary outcomes. Furthermore, it is unclear whether MS is an effective choice of analgesia for preterm ventilated infants.

Although MS is commonly used in the NICU for ventilated infants, there is still debate over its use and uncertainty about its effect on neonatal outcomes.[4,18] Based on the literature critiqued, there is no consensus on a preferred method to treat procedural and prolonged pain in preterm infants. It is uncertain whether preemptive MS improved, worsened, or even contributed to adverse neonatal outcomes in preterm infants. The APNN must make the best use of available information about the use of MS analgesia for the preterm infant, and use it to guide policy and practice for infants under his or her care. This task is made challenging when the research lacks clarity and certainty about the role of MS in pain in preterm infants.

Because of the lack of research consensus related to MS use in preterm infants, the APNN may implement alternative nonpharmacologic interventions such as facilitated tuck, nonnutritive sucking, and nonnoxious sensory stimulation to alleviate pain.[44,45] The NICU nurse plays a crucial role in best using such nonpharmacologic interventions previously mentioned that may minimize the effects of pain and stress during painful procedures and routine handling. Parental participation in the use of these pain reduction techniques, including kangaroo care should be encouraged and supported by NICU nurses.[46] Parental presence appeared to enhance use of pain management in infants in the NICU.[47] Thus, NICU nurses should encourage parental involvement in their infant's care in order to advocate for appropriate pain reducing strategies. The APNN must use his or her clinical expertise to judicially balance the risks and benefits of MS analgesia when used, and tailor the treatment plan to each infant's specific needs.

Als described the preterm infant as a displaced fetus surviving in a developmentally inapt environment outside the uterus.[48] An enhanced understanding and assessment of the pain experience and resultant behaviors in preterm infants may facilitate better pain management.[44] Using the Synactive Model of Neonatal Behavioral Organization as a framework to better understand neurobehavioral development in preterm infants, the APRN can better make decisions regarding the use of analgesics such as MS to decrease pain in preterm ventilated infants to minimize adverse effects of pain and support optimal neurodevelopment.[48]

Future research should be directed at gaps in knowledge of pain in preterm infants. It is important to determine whether adverse outcomes are related to MS use or reflective of an infant's predisposition to certain outcomes based on GA. Research should examine a preterm population with a narrow range of GA who are more likely to be similar in inherent morbidity risk. It is important to account for variation in individual setting practices related to preterm analgesia to enhance generalizability of data. Addressing these issues may yield more potent information about neurologic, pulmonary, or cardiovascular outcomes that can be used by the APNN to provide appropriate management of pain with MS and for the NICU nurse to deliver effective care for the preterm ventilated infant.

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Breastfeeding the Infant With Congenital Diaphragmatic Hernia Post Extracorporeal Membrane Oxygenation

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Abstract

Infants born with congenital diaphragmatic hernia (CDH) often require extracorporeal membrane oxygenation (ECMO). Infants on ECMO may experience a long period of being nothing by mouth (NPO) while receiving parenteral nutrition. Once the infant with CDH is repaired and off ECMO, human milk should be used to initiate enteral feedings. Human milk provides immunologic, developmental, and nutritional protection for these high-risk infants and may be crucial in decreasing morbidities commonly associated with post-ECMO survivors. These mother–infant dyads require extensive lactation support to ensure maintenance of milk supply and successful transition to direct breastfeeding. Three case studies are presented as exemplars to demonstrate how breastfeeding success can be achieved even in the most vulnerable infants.

Congenital diaphragmatic hernia (CDH) is an anatomical malformation in which the visceral abdominal contents herniate into the thoracic cavity via a discontinuity of the musculature of the diaphragm. Congenital diaphragmatic hernia is diagnosed in 1 case in every 2,000–5,000 live births and is associated with significant infant morbidity and mortality rates.[1] Although there have been several medical advancements (i.e., delayed operative repair, inhaled nitric oxide, high-frequency oscillatory ventilation, and extracorporeal membrane oxygenation [ECMO]) in the treatment of infants born with CDH, mortality rates, inclusive of hidden mortality (death before admittance to a treatment center), remain around 50 percent.[2] Infants diagnosed with CDH are cared for in the neonatal intesive care unit (NICU) setting. The necessary medical and surgical therapies unfortunately separate mother and infant and also subject the infant to a period without enteral feedings. It is during this time that the advantages of human milk may be most essential.

EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation provides cardiac and respiratory support to neonates who require the assistance. It is a modification of cardiopulmonary bypass technology.[3] Many reversible conditions, such as CDH, have altered ventilation or oxygenation, and thus patients may require ECMO instead of conventional ventilation as a temporary and radical intervention. Extracorporeal membrane oxygenation is specifically used for the neonate because of conditions including CDH, persistent pulmonary hypertension, meconium aspiration, and congenital heart disease.[4]

There are two methods of ECMO support for neonates: venous–arterial or venous–venous.[3] In both cases, blood is drained from the venous system, but it is reinfused through either the arterial or venous system depending on the method, the reinfusion, and the reinfusion site employed. Venous–arterial ECMO provides support for the heart and lungs, and cannulas are placed in the right internal jugular vein and the right common carotid artery

Disclaimer

This article is not intended to be a comprehensive review of every state's law, nor is it intended to provide legal advice. Seek legal counsel in the event you have questions regarding legal issues.

Accepted for publication July 2011.

http://dx.doi.org/10.1891/0730-0832.31.1.31

for a continuous blood exchange. An ECMO flow rate of 100 mL/kg is typically used to create an estimated 80 percent of an infant's cardiac output.[3] In the past, venous–arterial ECMO was the only method used, but now venous–venous ECMO is the preferred method.[3]

Venous–venous ECMO is used for infants with respiratory failure, and special double-lumen cannulas, designed only for neonates, are used for proper placement into the right internal jugular vein only (as opposed to accessing two separate veins). Since its start in the 1980s, ECMO has been used in more than 23,000 cases of respiratory failure in neonates and more than 29,000 patients worldwide.[3,5]

The ECMO process involves a membrane oxygenator, a heat exchanger, a circuit, and a pump.[3] Deoxygenated blood is drained from the patient and pumped into the membrane oxygenator for O_2 and CO_2 exchange to occur. Once gas exchange has occurred and the blood has been warmed by the heat exchanger, the newly arterialized blood is returned to the patient.[3] Extracorporeal membrane oxygenation is not intended to be a therapy but a supportive measure, and there are significant risks associated with ECMO. Most newborns with severe respiratory disease are considered for ECMO once they have greater than 80 percent risk of death determined by the oxygenation index.[3] The overall survival rate following ECMO therapy is approximately 76 percent, with meconium aspiration syndrome having the highest survival rate (94 percent) and CDH having the lowest survival rate (56 percent).[3]

Studies have indicated that ECMO survivors suffer from neurologic and respiratory morbidities as well as behavior problems.[5] In addition, many of the patients who receive ECMO require hospital readmission after discharge because of various infections and postoperation complications.[5] Human milk can protect the infant in three specific ways: infection protection, increased feeding tolerance, and developmental protection as highlighted in the next section. Because of the potential risks and long-term effects associated with ECMO, the use of human milk for post-ECMO neonates should be actively promoted and protected.

THE ROLE OF HUMAN MILK AND BREASTFEEDING

Extracorporeal membrane oxygenation requires a high protein catabolic rate. As a result, neonates can lose up to 15 percent of their lean body mass during seven days of ECMO.[4] Overall energy requirements of an ECMO patient and a healthy neonate are the same (100–120 kcal/kg/day); however, protein requirements may be up to 3 g/kg/day for an ECMO patient, as compared with the healthy neonate requiring 1.5 g/kg/day.[4,6] During ECMO, infants are generally supported only through parenteral nutrition. Once the patient's condition has improved and stabilized, enteral nutrition can be initiated.[4] Enteral nutrition in neonates stimulates intestinal hormone secretion, which can create positive changes in the gut mucosal integrity.[7] Enteral feeding tolerance is a key indicator for length of stay, and infants who have slow tolerance to enteral feeding have a 3.6-fold longer length of hospital stay.[4]

Human milk in the infant with CDH who has required ECMO support can protect the infant in three specific ways: protection against infection, improved feeding tolerance, and enhanced neurodevelopmental protection. There are many reported morbidities associated with the diagnosis and survivorship of CDH. Of greatest relevance are respiratory, gastrointestinal, and nutritional morbidities. Human milk has known anti-infective and nutritional properties that can benefit the infant with CDH. Human milk studies have shown protection against gastroenteritis, upper and lower respiratory tract infections, urinary tract infections, neonatal septicemia, necrotizing enterocolitis, and acute otitis media via passive immunity and prolonged immunologic support.[8–16]

Infants diagnosed with CDH suffer greater incidence of chronic lung disease, pulmonary hypertension, respiratory tract infections, pneumonia, bronchospasm, wheezing, asthma, obstructive and restrictive pulmonary function anomalies, and lung hypoplasia.[17–19] Furthermore, respiratory tract infections are reported in 25–50 percent of children with CDH in the first year of life.[17,19] A significant reduction in respiratory tract infections among infants fed a predominantly human milk diet has been demonstrated.[9,12,20,21] The anti-infective components of human milk (i.e., immune cells, long-chain polyunsaturated fatty acids, cytokines, nucleotides, proteins, hormones, and bioactive peptides) work in tandem to protect the infant from infection, therefore lowering the relative risk of respiratory-associated morbidities.[22] These findings support the case for an exclusive human milk diet in the CDH population.

Many infants diagnosed with CDH suffer from both long- and short-term gastrointestinal morbidities, including gastroesophageal reflux disease, malrotation, intestinal adhesions and obstructions, intestinal perforation, and gut dysmotility.[17,18,23–25] There are many theories that discuss the etiology of related gastrointestinal morbidities; however, often, the etiology can be linked to the size of the defect and the type of repair.[19] The nutritional and prebiotic aspects of human milk are important for the infant diagnosed with CDH. Human milk primes and supplements the infant gut with healthy bacteria. Glycans (including oligosaccharides), a major component of human milk, protect the infant by stimulating the growth of bifidobacteria and lactobacilli in the colon.[26] Concentrations of oligosaccharides are at their highest in the maternal colostrum.[27] Rodriguez, Meier, Groer, and Zeller describe the theoretical perspectives of the oropharyngeal administration in extremely low birth weight infants and note that the administration of colostrum may have an immunomodulatory effect on infants.[28] The infant may absorb the essential components (cytokines in particular) of the colostrum through the mucous membranes of the buccal cavity.[28,29] Furthermore, Rodriguez and colleagues demonstrated that oropharyngeal administration of colostrum is easy, inexpensive, and well tolerated by even the smallest and sickest infants (n = 5 infants with mean birth weight of

657 g and mean gestational age of 25.5 weeks).[30] Therefore, although the CDH infant may not be able to experience enteral feedings directly following birth, oral care can be done with the colostrum so that the infant can absorb the oligosaccharides via the oral mucosa.

Associated with the gastrointestinal morbidities, infants diagnosed with CDH often have issues related to nutritional development such as the development of oral aversions and the requirement for tube enteral feeding.[31,32] Frequently, infants with CDH develop oral aversions. Oral aversions can be described as behaviors that demonstrate a reluctance or refusal to eat by mouth (PO). It is suspected that the prolonged period of intubation is highly correlated to the incidence of oral aversion, and it is estimated that approximately 25 percent of surviving CDH infants show behaviors associated with an oral aversion.[33] Because of the oral aversion, infants may be poor oral feeders and, subsequently, approximately 30 percent of CDH survivors are required to have gastrostomy feeding tubes placed following their initial surgery.[1,33] It has been suggested that the presence of nasogastric and oral feeding tubes only increases oral aversion.[18] It is unknown whether oral aversion could be decreased with breastfeeding as compared with bottle feeding. When an infant feeds at the breast, he controls the flow of the milk, whereas in bottle feeding, the milk flows freely from the nipple. Breastfeeding allows the infant to regulate the amount of milk transferred as well as the amount of time spent at the breast actively feeding. During breastfeeding, the infant controls the flow of milk from the breast by vacuum exerted and suckling as compared with bottle feeding where the milk just flows; therefore, breastfeeding may decrease oral aversion in this population. Future research is warranted to examine the incidence of oral aversion comparing bottle feedings with breastfeedings among CDH infants post-ECMO.

SUPPORTING BREASTFEEDING IN POSTEXTRACORPOREAL MEMBRANE OXYGENATION NEONATES

The 10-step process for vulnerable infants (Table 1) can ensure lactation and breastfeeding success.[34] These steps were developed by the author because the World Health Organization's "Baby-Friendly Hospital Initiative (WHO/UNICEF Ten Steps to Successful Breastfeeding)" only meet the needs of healthy term infants. Mothers with infants in the NICU experience a very different breastfeeding process. These steps were developed from the research literature and implemented in clinical practice yielding positive breastfeeding outcomes. Edwards and Spatz further developed the ten-step process into a transition to breast pathway that included five key elements to ensure breastfeeding success in infants born with complex surgical anomalies.[29] These five components are (1) initiation of lactation and maintenance of milk supply, (2) oral care with colostrum and human milk, (3) skin-to-skin contact, (4) nonnutritive suckling at the breast, and (5) direct breastfeeding.[29]

TABLE 1 ■ Ten Steps to Promoting and Protecting Breastfeeding for Vulnerable Infants[34]

1. Informed decision	Parents of critically ill infants must be educated regarding the science of human milk and how human milk can improve short- and long-term health outcomes of their child.
2. Establishment and maintenance of milk supply	Mothers should initiate pumping ideally within the first 2–4 hours after delivery and pump every 2–3 hours with a goal of eight pumps per day. A pumping log should be kept and reviewed daily by the infant's nurse. Mothers should be given a goal for milk production of 500–1,000 mL/day.
3. Breast milk management	Human milk should be properly labeled and stored to ensure its safety and that the right baby receives the right milk.
4. Feeding of breast milk	Begins with oral care: The parent or nurse dips a sterile cotton- swabbed applicator into fresh breast milk and then coats the inside of the infant's buccal mucosa while the infant is NPO. When initiating enteral feedings, colostrum should always be used first for 24–96 hours. After this, fresh milk feedings should be prioritized.
5. Skin-to-skin care	Once the infant is stable and can be moved out of bed, the parent holds the infant with direct skin-to-skin contact between parent and infant.
6. Nonnutritive sucking at the breast	While doing skin-to-skin care, the infant suckles at the mother's empty breast, "practicing" for nutritive breastfeedings.
7. Transition to breast	The mother transitions from nonnutritive sucking at the breast to active breastfeeds.
8. Measuring milk transfer	Preweights and postweights (test weights) are essential for measuring milk transfer when the infant begins breastfeeding. The infant is weighed prior to the start of the feed and directly following the feed on a precise electronic scale.
9. Preparation for discharge	Encourage the mother to visit all day or all night and feed the infant based on his or her cues while doing preweights and postweights after each feedings.
10. Appropriate follow-up	The mother will need to continue to pump at home until the infant is fully efficient at the breast. The mother will need to rent a BabyWeigh scale at home in order to measure milk transfer. Provide mother with a 24-hour intake goal based on the infant's weight.

Key: NPO = nothing by mouth.

The first step requires a mother to make an informed choice to initiate pumping because she fully understands the health benefits of human milk. Initiation of lactation via mechanical expression is crucial to the mother of an infant with CDH who requires ECMO. Ideally, the mother should initiate pumping within two to four hours after delivery. Mothers should be instructed to pump with a hospital grade pump every two to three hours with a goal of achieving eight pumping sessions per 24-hour period.[34] By the end of the first week, the goal for milk production

should be 500–1,000 mL/24-hour period.[34] Using a visual guide or pump log will allow both the nurse and mother to ensure milk production is being established and maintained throughout the infant's hospitalization.[29,34]

Oral care involves dipping a sterile cotton-swabbed applicator in colostrum, or mature human milk, and coating the entire inside of the infant's buccal mucosa with the milk.[29] Newborns are able to absorb some of the cytokines from the milk via their buccal mucosa, thus providing them with an immunologic boost.[28] Oral care can be initiated as soon as the mother has drops of colostrum available, even while the infant is on ECMO.[29] Mothers should be encouraged to pump at their infant's bedside and perform oral care each time that they pump prior to freezing the milk to save for later use. Oral care may be an important intervention to decrease the risk of infection during the time when the infant is nothing by mouth (NPO).[30]

Once the infant is repaired and post-ECMO, skin-to-skin contact must be the priority for the mother–infant dyad. Skin-to-skin contact increases maternal milk volume and facilitates the production of maternal antibodies.[35] Once the infant is extubated, nonnutritive sucking at the breast should be initiated.[29] The mother should be instructed to pump first to empty her breasts to prevent the infant from transferring milk until the infant is able to tolerate oral feedings.[29]

As the infant progresses with enteral feedings and participates in skin-to-skin contact and nonnutritive sucking at the breast, the plan for oral feedings should be established. Breastfeeding should be viewed as the priority because of the decreased risk for apnea and bradycardia as compared with bottle feeding.[35]

The nurse is essential in ensuring that the mother is achieving her pumping and milk volume goals. Each day, the nurse should review the mother's pumping log even during the time when an infant is critically ill and NPO. The nurse is the first line of defense to troubleshoot pumping or milk supply concerns or questions. As soon as the mother has drops of colostrum available, the nurse can teach the parents how to perform oral care with human milk. The nurse should encourage the family to perform oral care each time the mother pumps at her infant's bedside. In addition, the nurse can ask the mother to leave a small volume (5 mL) of milk when the mother is not present for the nurse to perform oral care when the nurse does the infant's routine care.

The nurse also directs when skin-to-skin care contact can be initiated and she can empower the family to hold their infant skin to skin as often as possible. Once the infant is extubated, the nurse should assist the mother with nonnutritive sucking as a preparation for breastfeeding. The provision of human milk and breastfeeding the infant with CDH requires continual education, reassurance, and technical and emotional support by the nurse. This commitment will ensure that even the most vulnerable infants can benefit from human milk and have the opportunity to breastfeed if that is the mother's goal.

CASE EXEMPLARS OF BREASTFEEDING SUCCESS

Case Exemplar A

The mother of Baby Girl A is a 39-year-old, gravida 2, para 2, woman with lactose intolerance and no other significant medical history or breast trauma/surgery. She had previous breastfeeding experience with an estimated milk supply of 400 mL/day with her first child. Following the diagnosis of CDH in her fetus, this mother had a prenatal lactation consult 45 days before her Estimated Date of Confinement (EDC). During this consultation, the importance of the provision of human milk was discussed and instruction of the following was provided: (1) initiation of lactation via pumping, (2) cleaning/labeling/storing of breast pumping supplies, (3) types of pumps, (4) pump rental, and (5) breast milk labeling and storage. The mother was also given a logbook, handouts, and the 10 steps to promoting and protecting breastfeeding for vulnerable infants.[34] The mother's goal was to provide human milk and/or breastfeed for one year. In order to meet this goal, the plan for the mother of Baby Girl A was to focus on early and frequent pumping to establish milk supply.

Baby Girl A was delivered vaginally at the Children's Hospital of Philadelphia (CHOP) Special Delivery Unit (SDU) at 39 weeks gestation. The infant was stabilized and transferred to the CHOP NICU for continued support and ECMO. The mother's next lactation consult was on Baby Girl A's fifth day of life (DOL). At this point in time, the infant was NPO, on ECMO, and intubated, and her mother was doing oral care with her breast milk. Her daily log is outlined in Table 2. The plan of care for Baby Girl A involved a scheduled repair of her CDH on DOL 6. Following Baby Girl A's successful surgical repair, the mother received her

TABLE 2 ■ Exemplar Case A's Daily Log

Infant's Day of Life	Number of Pumps/Day	Milk Supply (in mL/day)	Milk Transfer/ BF Session (in g)
1	1	3	
2	7	3	
3	6	0	
4	7	19	
5	7	119	
6	5	132	
7	7	246	
8	7	348	
9 (2nd postpartum consult)	8	428	18
14 (3rd postpartum consult)	8	1,200	50
19 (4th and final lactation consult)	6	700	54

Key: BF = breastfeeding.

second postpartum lactation consult (baby's DOL 9). Baby Girl A had been repaired three days prior, was off ECMO, and was now receiving enteral feedings of 5 mL maternal breast milk (MBM) every three hours via a nasogastric feeding tube. The plan for her mother was to maintain her milk supply and to encourage skin-to-skin care and nonnutritive sucking. Between Baby Girl A's DOL 9 and DOL 14, she transitioned from trophic feedings to enteral feedings (including PO feedings) of 50 mL MBM every three hours. Additionally, during these five days, she had taken several feedings by bottle and had fed at the breast numerous times, transferring between 18 and 50 mL with each breastfeeding. Baby Girl A was latching well at the breast and the plan for the mother and infant was to continue breastfeeding as much as possible and for the mother to continue pumping. The mother's milk supply at this time was approximately 150 mL/pump or about 1,200 mL/day. The final hospital lactation consult for the mother of Baby Girl A was on DOL 19. Baby Girl A was taking between 60 and 65 mL of MBM every three hours. During this final consultation, the lactation consultant was able to observe Baby Girl A at the breast and she transferred 54 mL from her mother's breast.

This mother continued to breastfeed posthospital discharge using a Medela Pump in Style Advanced breast pump and a Medela BabyWeigh scale (to measure the infant's milk transfer at the breast) at home. In the first months postdischarge, she continued to both breastfeed and bottle feed expressed milk. The mother ultimately was successful in breastfeeding her daughter for 11 months and one week (three weeks shy of her one-year goal). The mother reported that her daughter was in general very healthy during her first year of life and was followed regularly as an outpatient as part of the standard follow-up for CDH infants. The infant was not rehospitalized during her first year of life post the initial hospitalization.

Case Exemplar B

The mother of Baby Girl B is a 32-year-old, gravida 4, para 1, woman with no significant medical history or breast trauma or breast surgery. This pregnancy was the result of *in vitro* fertilization. She had no previous breastfeeding experience and limited breastfeeding knowledge prior to her prenatal lactation consult. The mother of Baby Girl B was seen prenatally 27 days before her EDC to discuss the importance of the provision of human milk for her infant. The standard of care at our institution is that all mothers have a prenatal lactation consultation. The rationale for this is that our focus is on the provision of human milk versus breastfeeding *per se*. The provision of human milk is viewed as an intervention like any other intervention in the NICU. By seeing all mothers prenatally, women can make an informed choice and also have the necessary knowledge and equipment to initiate pumping immediately (within two to four hours of delivery). During her consult, the same instruction and handouts were provided as with the case of Baby Girl A. The mother of Baby Girl B had a goal to provide human milk for "as long as possible" with hopes of transitioning to breastfeeds. This mother decided to rent a Medela Symphony breast pump postdelivery.

Baby Girl B was born vaginally via induction in the CHOP SDU. She was 39 weeks and one day gestation at the time of delivery and weighed 6 lbs. 2 oz. The infant was stabilized and transferred to the CHOP NICU for continued support and care. The mother's initial postpartum lactation consult was on Baby Girl B's DOL 3, the same day her baby was put on ECMO. Prior to this consult, the mother had been instructed to mechanically pump her breasts every two to three hours, perform oral care, and save the remaining colostrum in the freezer for later use for enteral feedings. On DOL 3, Baby Girl B was NPO and her mother was doing oral care using sterile cotton swabs dipped in her colostrum. Her mother was pumping eight to ten times per day and on DOL 3, milk supply was at 10 mL in a 24-hour period. On DOL 4, Baby Girl B's mother suffered from mild skin breakdown around her nipples and it was recommended that she increase the flange size she was using with her pump. She was encouraged to continue pumping every two to three hours. Baby Girl B's mother had her third postpartum lactation consultation on DOL 10, voicing concern of low milk supply (~300 mL/day even though she continued to pump eight to ten times per day). At this point, Baby Girl B's mother was counseled regarding low milk supply and given a patient family education sheet. Additionally, she was counseled to start domperidone. Research on domperidone demonstrates both its safety and efficacy in increasing milk supply.[36] Baby Girl B's mother started domperidone 20 mg PO three times per day on her infant's DOL 26. She also had her thyroid examined and the results were all within normal limits.

Baby Girl B remained on ECMO therapy for 32 days and was NPO throughout. Her mother and father were very diligent with oral care and her mother continued pumping every two to three hours. On the baby's DOL 41, her mother had her sixth postpartum lactation consultation. Baby Girl B had been surgically repaired and off ECMO for five days but was NPO on this day for a magnetic resonance imaging (MRI), although she had started trophic feedings following her repair. Enteral feedings were again started following her MRI. Baby Girl B's mother continued to pump about eight times per day and her supply remained approximately 230 mL/day. However, she was suffering from overwhelming stress and anxiety. The lactation consultant reassured her and encouraged her to continue with oral care and to begin preparing for skin-to-skin care.

On Baby Girl B's DOL 53, her mother was seen for her seventh consultation. Baby Girl B had made great progress since the last consultation. She was working up on her total volume of enteral feedings via her nasogastric feeding tube. Baby Girl B had been skin to skin with her mother and father several times each day and she had practiced nonnutritive sucking at her mother's breast. The infant was now allowed

to begin attempting PO feeding and had reached a volume of 60 mL of fortified MBM 24 kcal/oz every three hours PO or by nasogastric feeding tube. Her mother had noticed a significant improvement in her milk supply over the past few days and attributed that to her infant's status and the skin-to-skin care. Later on the same day, Baby Girl B went to breast. She had an uncoordinated sucking reflex but did swallow a few times at the breast. The plan was to continue putting the baby to breast one to two times per day, continue with skin-to-skin care, and for her mother to continue pumping every three hours. Two days later, Baby Girl B had her first successful milk transfer. She transferred 4 mL of milk from her mother's breast. By DOL 56, Baby Girl B was able to transfer 10 mL. And on DOL 69, she transferred 20 mL during one breastfeeding session. This mother's log is detailed in Table 3.

Baby Girl B's mother struggled with maintaining her milk supply throughout the baby's hospitalization. She continued to pump eight to ten times per day and increased the domperidone to the maximum dosage of 20 mg four times per day. With the mother's diligence in pumping and pharmacologic intervention, her milk supply was maximized at approximately 300 mL/day, which allowed her to establish an extensive frozen milk supply during the long period when Baby Girl B was NPO and on ECMO. However, frequent assessments and consultations reassured and motivated this mother to continue on the breastfeeding pathway. Her baby spent 32 days on ECMO yet still transitioned to breastfeeds. By the time of discharge, Baby Girl B was transferring on average 20–30 mL of human milk from her mother's breast with each breastfeeding session.

Postdischarge, Baby Girl B remained on both tube feeds and breastfeeds. Her mother rented a BabyWeigh scale to assess milk transfer at home. Baby Girl B's mother continued the regimen of pumping, tube feeding, and breastfeeding and was able to provide her daughter with human milk for 9.5 months.

Case Exemplar C

Baby Girl C was born to a 34-year-old, gravida 3, para 3, African-American woman with a positive past lactation history. She breastfed her two older daughters: one for five months and the other for eight months. Following prenatal diagnosis of CDH during the beginning of her third trimester, the mother transferred her care to the CHOP and relocated to Philadelphia in her third trimester for delivery at CHOP. Prior to delivery, this mother also received a prenatal lactation consultation as per our standard of care. The mother was induced at 38 or more weeks and had a cesarean delivery for failure to progress. The infant was 6 lbs. 6 oz. at birth.

The mother began pumping on delivery day using a hospital grade Medela Symphony pump with the Preemie Plus pumping pattern to establish her milk supply. She also began doing oral care with her colostrum on DOL 1 postdelivery.

TABLE 3 ■ Exemplar Case B's Daily Log

Infant's Day of Life	Number of Pumps/ Day	Milk Supply (in mL/ day)	Milk Transfer/ BF Session (in g)
1	2	0	
2	8	drops	
3 (1st postpartum consult)	7	18.5	
4 (2nd postpartum consult)	7	57.5	
5	7	136	
6	7	162	
8	8	194	
9	7	195	
10 (3rd postpartum consult)	9	239	
11	8	234	
12	8	261	
13	8	250	
14	8	260	
15	6	262	
16	7	260	
17	7	273	
18 (4th postpartum consult)	8	287	
19	7	275	
24 (5th postpartum consult)	8	270	
41 (6th postpartum consult)	8	230*	
53 (7th postpartum consult)	8	300†	
54 (8th postpartum consult)	8	300†	
55 (9th postpartum consult)	8	300†	4
56 (10th postpartum consult)	8	250†	10
60 (11th postpartum consult)	8	275†	4
61 (12th postpartum consult)	8	300†	0
62 (13th postpartum consult)	8	300†	0
66 (14th postpartum consult)	8	300‡	10
69 (15th postpartum consult)	8	350‡	20
70 (16th postpartum consult)	8	350‡	32
74 (17th postpartum consult)	7	300‡	22
75 (18th postpartum consult)	7	300‡	12
76 (19th postpartum consult)	8	300§	10
81 (20th postpartum consult)	8	300§	26
82 (21st postpartum consult)	8	300§	10
83 (22nd postpartum consult)	8	300§	30
90 (final consult)	8	300§	20

Key: BF = breastfeeding; PO = by mouth; TID = three times a day; QID = four times a day.

*Domperidone 20 mg PO TID.

†Domperidone 30 mg PO TID.

‡Domperidone 40 mg PO TID.

§Domperidone 20 mg PO QID.

TABLE 4 ■ Exemplar Case C's Daily Log

Infant's Day of Life	Number of Pumps/Day	Milk Supply (in mL/day)	Milk Transfer/BF Session (in g)
4 (1st postpartum consult)	6	323	
13 (2nd postpartum consult)	8	800	
34 (3rd postpartum consult)	7	850	
57 (4th postpartum consult)	7	1,000	
67 (5th postpartum consult)	6	900	18
81 (6th postpartum consult)	7	900	24–30

Key: BF = breastfeeding.

By the DOL 4, she was producing more than 300 mL of milk per day. The neonate required ECMO, and she was on ECMO for 10 days. The mother continued to pump seven to eight times per day and produced approximately 800 mL per day.

By DOL 34, the infant was advancing feedings at 13 mL human milk every three hours via nasogastric tube. The mother continued to pump six to seven times per day for an average of 850 mL per day. By DOL 57, the infant was up to 65 mL per day every three hours via nasogastric tube and the mother was still pumping six to seven times per day and making more than 1 liter of milk per day. During this time, the mother did nonnutritive sucking with the infant during tube feedings, usually once per day. By DOL 67, the infant began breastfeeding. The infant transferred between 2 and 30 g at the breast using a nipple shield. By DOL 68, the infant continued to breastfeed several times per day and transferred between 24 and 30 g at the breast (Table 4).

The infant was discharged at DOL 81 with a nasogastric tube in place. The discharge plan was for the mother to breastfeed the infant at the breast whenever the infant was alert and interested. If the baby could not be fed from the breast, then the baby would be fed via the nasogastric tube. The mother was instructed that the baby needed a minimum of 680 mL of human milk per day based on her weight at discharge. The mother was instructed to follow the infant's feeding cues. The mother continued to rent a hospital grade pump for home and she also rented a BabyWeigh scale to measure milk transfer. At home, the mother continued the regimen of pumping, tube feeding, and breastfeeding, and the infant received exclusive human milk for the first six months of life and the mother continues to breastfeed.

CONCLUSION

With sound research-based support and care, all three of these mothers were able to reach their personal breastfeeding goals. In addition, all three of these infants received exclusive human milk for at least the first six months of life (including stored frozen MBM and for Baby Girl B, supplementary donor milk). This is remarkable given that less than 14 percent of infants in the United States are exclusively breastfed for six months.[37] Infants born with CDH who have undergone ECMO treatment face a long and challenging road of recovery ahead. Human milk and breastfeeding can provide unique protection for these high-risk infants and should be viewed as an essential component of nursing care for these infants.

NICU nurses are the key health professionals who can ensure that even the most vulnerable infants receive human milk and have the opportunity to breastfeed if that is the mother's goal. It is essential that nurses receive adequate lactation and breastfeeding education and training to ensure evidence-based lactation support and care to mothers of NICU infants.[38] Mothers of CDH infants must alter the traditional notions of breastfeeding to successfully transition their infants to breastfeeds. By following a transition to breast pathway, the bedside nurse can facilitate breastfeeding success.[29]

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Glucose-6-Phosphatase and Glucose-6-Phosphate Dehydrogenase Deficiency: How Are They Different?

Lori Baas Rubarth, PhD, NNP-BC

GLUCOSE-6-PHOSPHATASE and glucose-6-phosphate dehydrogenase (G6PD) are both important enzymes; a deficiency of either of these enzymes can cause the infant to have significant or life-threatening symptoms. Glucose-6-phosphatase deficiency is a glycogen-storage disease resulting in hypoglycemia and glycogen buildup in the liver that interferes with fat metabolism. G6PD deficiency is an X-linked hereditary disease resulting in nonimmune hemolytic anemia and jaundice. These two diseases sound so similar but are very, very different.

GLUCOSE-6-PHOSPHATASE DEFICIENCY

Glucose-6-phosphatase is a liver enzyme, which is necessary to break down glycogen into glucose to be used by the body, a process referred to as *glycogenolysis* (Table 1). The glycogen stored in the liver is broken down into glucose-1-phosphate and then into glucose-6-phosphate. In the presence of the enzyme glucose-6-phosphatase, a phosphate is removed (dephosphorylation) and the free glucose is released into the bloodstream (Figure 1). In most cells of the body, "the phosphorylation of glucose [or binding with phosphate] is almost completely irreversible except in the liver cells, the renal tubular epithelial cells, and the intestinal epithelial cells" (p. 831).[1] Therefore, phosphorylation keeps the glucose inside most cells of the body, but within the liver, the glucose-6-phosphatase enzyme reverses the phosphorylation reaction and releases glucose back into the bloodstream. This occurs more readily at birth with a rise in the glucose-6-phosphatase enzyme, converting the glycogen in the liver to glucose. The newborn's body mobilizes the glycogen into glucose just when glucose from the mother is no longer available. In the preterm or low birth weight infant, there has been shown to be a decrease in the glucose-6-phosphatase enzyme activity levels, which can contribute to the hypoglycemia seen in the preterm or low birth weight infant.[2] This lower level of glucose-6-phosphatase has also been seen in term infants who died of sudden infant death syndrome.[3]

Glycogen storage diseases (GSDs) result from inborn errors of glycogen metabolism. There are many types of GSDs. Glucose-6-phosphatase deficiency (or GSD type 1a) is a rare form of GSD, also called *von Gierke's disease*, and is an autosomal recessive genetic disorder. Parents who are heterozygous for the gene (asymptomatic carriers) have a 1:4 chance of having a child with the disease. In the absence of the glucose-6-phosphatase enzyme, glycogenolysis cannot occur and glycogen builds up within the liver cells and is not available for normal glucose needs, resulting in a drop in the blood glucose level and an increase in liver size. A buildup of glucose-6-phosphate also occurs and, via the glycolysis pathway, causes a rise in the infant's lactate level.[4]

Glucose-6-phosphatase deficiency is characterized by hypoglycemia, lactic acidosis, failure to thrive, and liver enlargement. Many newborns with GSD type 1a are asymptomatic (or "can appear healthy") at birth, but within the first few days of life, and with no glucose-6-phosphatase activity, fasting hypoglycemia develops and lactate levels increase. The resulting lactic acidosis can cause signs of respiratory distress as the infant attempts to compensate by breathing rapidly.[4] Hypoglycemia can go undetected in the newborn period because some infants with hypoglycemia do not exhibit symptoms. If symptoms do occur, they are the same as for any other type of hypoglycemia (Table 2). Infants with GSD type 1a may also present with an enlarged liver caused by the accumulation of glycogen in the liver. Glycogen accumulation begins during fetal life and, therefore, can cause a noticeably enlarged abdomen during the newborn period. Hepatomegaly will eventually occur even if not present in the newborns.[4]

Infants with persistent hypoglycemia, low insulin levels, high cortisol levels, high lactate levels, and hepatomegaly (with normal bilirubin and liver enzymes) require a workup for glucose-6-phosphatase deficiency and the other GSDs.[5] This disorder can be diagnosed during the first few days to weeks of an infant's life if practitioners are alert to the symptoms of an enlarged liver with persistent hypoglycemia. Treatment of these infants in the neonatal intensive care unit (NICU) begins with continuous glucose infusion for hypoglycemia and/or continuous tube feedings to maintain normal glucose levels.[4]

Long-term consequences of this disorder are liver damage, kidney failure, short stature, and brain injury. Avoidance of fasting and subsequent hypoglycemia is the goal of treatment to prevent brain injury. Older children are treated with a cornstarch type of infusion at night to prevent hypoglycemia. Other complications in these children and adults are high serum triglyceride and cholesterol levels, high uric acid levels (gout),

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Accepted for publication June 2011.

http://dx.doi.org/10.1891/0730-0832.31.1.45

TABLE 1 ■ Definitions

Dephosphorylation = the removal of a phosphate molecule by a phosphatase enzyme
Glycogenesis = glucose added together to make glycogen and stored in the liver or muscle
Glycogenolysis = glycogen broken down into glucose in the liver or muscle tissue (Glucagon and epinephrine can stimulate glycogenolysis.)
Glycolysis = the conversion of glucose to pyruvate to produce energy (2 ATP)
Gluconeogenesis = converts lactate (or other noncarbohydrate sources like glycerol or certain amino acids) into pyruvate and then into glucose within the liver
Phosphorylation = the addition of a phosphate molecule by a kinase enzyme

and renal calcifications leading to failure. Liver adenomas can further complicate the hepatomegaly in some patients leading to liver resection and/or transplantation.[6] Although this is a rare defect, the complications of the disease can be devastating, and glucose regulation in the newborn is a key to prevention of some of the more severe long-term problems.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

G6PD is an enzyme that converts or oxidizes glucose-6-phosphate into -6-phosphogluconate. The result of this process is an increase in the supply of reduced glutathione (GSH) in cells. GSH is an important antioxidant in the body because it eliminates the free radicals that cause oxidative injury. The reduced GSH can convert many harmful substances to nonharmful substances; for example, it converts hydrogen peroxide to water.[7] Without G6PD, there would be a limited amount of GSH and less antioxidant activity. This pathway for GSH is the only way that the red blood cells (RBCs) obtain the reduced form of GSH; without it, the infant is at risk for hemolytic anemia. The RBC can undergo hemolysis during periods of oxidative stress. Hemolysis results in the destruction of the RBC and high levels of indirect bilirubin.

FIGURE 1 ■ Glycogen to glucose.

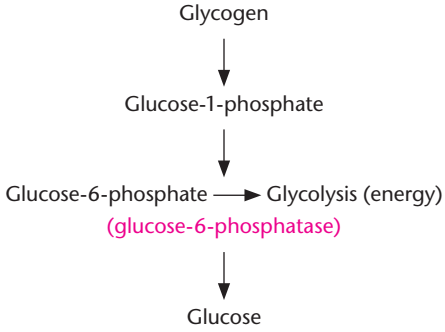

TABLE 2 ■ Symptoms of Hypoglycemia in Newborns

Jitteriness
Tremors
Irritability
Lethargy
Hypotonia
Apnea
Seizures
Refusal to suck

G6PD is an enzyme involved with RBC metabolism and cellular integrity. G6PD deficiency is an X-linked hereditary disease, meaning it is passed through the mother and affects male infants more severely, although women who carry one normal gene and one abnormal gene can be mildly affected. A female can have a severe case of the disease if she has two abnormal genes (which means her mother was a carrier with one abnormal gene and her father also had the disease). This is seen in populations with a high number of people with G6PD deficiency.[7]

A deficiency in G6PD results in prolonged hyperbilirubinemia in newborns. This prolonged high bilirubin level can cause kernicterus, which is a very serious, although rare, complication of G6PD deficiency. Newborns may be asymptomatic at birth and into the newborn period, or they may exhibit prolonged or high levels of jaundice, splenomegaly, or acute hemolytic anemia.

Male infants are at risk for G6PD deficiency if they are of African, Southeast Asian, or Mediterranean descent. The risk groups include Chinese, Greek, Italian (especially Sardinian and Sicilian), and Sephardic Jew (especially Syrian and Iranian).[8] A number of screening programs have been developed in the United States in areas with high populations of at-risk groups. These programs have been developed to decrease the incidence of kernicterus. By asking the parents about their ethnic backgrounds, nurses and physicians can be better prepared to look into G6PD as a cause for the infant's jaundice when appropriate. Infants in these risk categories should be treated for hyperbilirubinemia earlier and at lower levels than the usual American Academy of Pediatrics recommendations. An exchange transfusion to prevent kernicterus may be required if the jaundice becomes severe.

There are different variants of this disease from patients with chronic hemolytic anemia to patients with mild hemolysis with stressors only. One way to prevent the hemolysis and severe anemia is by avoiding oxidant medications, certain foods, infections, and broad beans (fava beans). Patients with favism have a deficiency of G6PD, but not all patients with G6PD have favism.[7]

CONCLUSIONS

We have discussed two very different disorders that sound alike, but affect infants in very different ways (Table 3).

TABLE 3 ■ Comparison of Glucose-6-Phosphatase Deficiency and Glucose-6-Phosphate Dehydrogenase Deficiency

	Glucose-6-Phosphatase Deficiency	Glucose-6-Phosphate Dehydrogenase Deficiency
Inheritance pattern	Autosomal recessive	X-Linked
Common signs	Hypoglycemia Enlarged liver Lactic acidosis	Jaundice RBC hemolysis Splenomegaly possible
At risk groups	Both male and female Caucasian Caucasian-Mediterranean	Primarily men Mediterranean Asian Nigerian/African American Greek Syrian
Diagnosis	Liver biopsy	Enzyme assay (Newborn screen)
Treatment	Avoid fasting	Avoid oxidative stressors

Glucose-6-phosphatase deficiency results in hypoglycemia and an enlarged liver. G6PD deficiency results in hyperbilirubinemia and anemia. These are important disorders to explore in order to prevent brain damage from hypoglycemia and hypoxia or from kernicterus. Both disorders can have devastating consequences. Infants with both of these disorders may appear asymptomatic at birth—totally healthy. The disorders may be difficult to diagnose early, but if we miss the early signs, the infants can develop worse prognoses.

A newborn has hypoglycemia when his intravenous glucose is weaned or when he continues to have low sugars despite adequate enteral feedings. What should you do? Check his liver. How big is it? An African-American, male newborn has a bilirubin that is higher than normal on day 2 of life, prior to discharge. What is his hematocrit? Are you more concerned because of his race, nationality, or ethnic background? The next infant that you care for in the NICU with prolonged jaundice or chronic hypoglycemia may warrant further exploration.

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Effect of Therapeutic Hypothermia on Drug Metabolism

Susan Givens Bell, DNP, MABMH, RNC-NIC

THERAPEUTIC HYPOTHERMIA is increasingly used for neonates older than 36-weeks gestation who meet specific criteria following an apparent, acute perinatal hypoxic or ischmeic event.[1] In their systematic review of eight randomized controlled trial of therapeutic hypothermia, which included 638 newborn infants, Jacobs and associates concluded that therapeutic hypothermia reduces death or disability in term newborns who have suffered a hypoxic episode around the time of birth.[2] With increased application of therapeutic hypothermia, it is important to understand the impact of this therapy on other therapies used concomitantly. In a recent review of the literature, Tortorici and colleagues found that the therapeutic hypothermia has an effect on drug metabolism, elimination, and response.[3] However, because there maybe a different response depending on the class of the drug, generalizations about adjusting dosing cannot be made. This column will review aspects of drug metabolism and relevant studies of the metabolism specific drugs in human neonates treated with hypothermia. Because few studies have addressed the effects of hypothermia on drug metabolism in neonates, this area is ripe for research.

DRUG METABOLISM

Drug metabolism is one of the four pharmacokinetic processes. The others are absorption, distribution, and excretion. (For a more in-depth discussion of these concepts, see the Pointers in Practical Pharmacology column in the January/February, 2011, issue of *Neonatal Network*).[4] Approximately 80 percent of the drugs that undergo metabolism in the body are metabolized in the liver by the cytochrome P450 system.[5] During phase I reactions, drugs are converted to more water-soluble forms or to more reactive forms in the liver. The enzymes of the cytochrome P450 system are responsible for most of these changes.[6] Many of these reactions are oxidation or reduction reactions (redox reactions) that remove or add oxygen and hydrogen to and from the drug molecules.[7] Conjugation occurs during phase II reactions. Conjugation is the addition of a chemical group, such as glucoronate or acetate, to the drug molecule, making the conjugate—the resulting metabolites—even more water-soluble.[6] As a result of phase II reactions, drug metabolites are generally inactive and are rapidly excreted in the urine and feces.[8] Phase I metabolism is reduced in neonates because of physiologic immaturity and increases over the first 6 months of life.[9]

From their review of the literature, which included studies across the range of ages from neonates to adults, Tortorici and colleagues concluded that CYP450 enzyme activity is reduced during cooling.[3] For example, in a model of warm-adapted and cold-adapted orthologs (genes from different species with a common ancestor[10]), Somero found decreased binding ability of multiple enzyme isoforms.[11] Tortorici and colleagues suggested that a potential mechanism for hypothermia-induced changes in cytochrome P450-mediated metabolism is changes in the binding confirmation of the enzymes.[3] Additionally, hypothermia may decrease the affinity of cytochrome P450 enzymes for some drugs. Finally, hypothermia may slow redox reactions carried out by the cytochrome P450 system during phase I reactions.[3]

Few articles have been published on the effects of hypothermia on drug metabolism in the neonate—a MEDLINE search for articles published between 2007 and 2011 revealed one study on each of the following drugs: topiramate, phenobarbital, gentamicin, and morphine. These studies are reviewed in the following section.

REVIEW OF THE LITERATURE

A MEDLINE search using the keywords hypothermia, induced hypothermia, drug metabolism, pharmacokinetics, and neonates, and limiting the results to 2007–2011, returned four studies that specifically evaluated drug metabolism in neonates undergoing therapeutic hypothermia.[12–15]

Topiramate (TPM [Topamax; Janssen-Cilag; Cologno Monzese, Milan, Italy]) is a possible neuroprotective agent that has been evaluated for safety among infants treated with hypothermia for hypoxic-ischemic encephalopathy (HIE).[16] Filippi and colleagues studied the pharmacokinetics of TPM in a pilot study of 13 neonates treated concurrently with hyperthermia for HIE.[12] The 13 neonates were treated with total body deep hypothermia (DH; 30–33°C) or mild hypothermia (MH; 33–34°C) initiated within 6 hours of birth and maintained for 72 hours—the current standard of practice is a desired core temperature of 33°C for a neonate undergoing therapeutic hypothermia. To qualify for cooling, the neonates had to be greater than or equal to 36-weeks gestational age with a birth weight of greater than or equal to 1,800 g with at least one of the following criteria:

1. Apgar score less than or equal to five at 10 minutes;
2. continuing need for resuscitation, including endotracheal intubation or mask ventilation for more than 10 minutes after birth; or

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Accepted for publication July 2011.

http://dx.doi.org/10.1891/0730-0832.31.1.48

3. an umbilical cord blood, arterial, venous, or capillary blood gas with a pH less than or equal to 7 and base deficit less than or equal to −16 mmol/L within 60 minutes of birth.

In addition, the neonates have to exhibit signs of moderate to severe encephalopathy.[12]

The infants received TPM as enteric-coated granules mixed with water 5 mg/kg/day via orogastric tube. TPM dosing started at the beginning of hypothermia and continued for the first 3 days of life. The researchers chose this schedule arbitrarily under the assumption that hypothermia would not prevent TPM absorption, but would reduce TPM clearance.[12]

In adult patients with normal renal function, oral TPM reaches steady state in 4–5 days.[17] A drug is at steady state when the amount of drug administered during a period equals the amount of drug eliminated in the same period.[18] Because the patients in this study were treated with hypothermia and received TPM for only 72 hours, the researchers considered the TPM researched "virtual" steady state if the plasma concentration at 72 hours was within the concentration at 48 hours ± 10 percent.[12] The authors did not provide further explanation regarding the rationale for this definition of "virtual" steady state in these patients. Mean TPM concentration was calculated for all 13 of the infants. Nine of the 13 infants enrolled in the study reached the virtual steady state. In these infants, maximal plasma concentration (C_{max}), minimal plasma concentration (C_{min}), time of peak concentration (T_{max}), and area under plasma concentration–time curve from 0–24 hours (AUC_{0-24})—that is, the amount of drug in the plasma from 0–24 hours—were derived. Drug half-life ($T_{1/2}$), the average plasma concentration (C_{avg}) during the 24-hour dosing periods, and apparent oral clearance were also derived or calculated.[12]

There were three female and ten male infants enrolled in the study. Five of the infants were treated with DH; eight infants were treated with MH. The initial dose of TPM was administered at 4.3 ± 1.3 hours. Phenobarbital was initiated at 4.5 ± 1 hours for the seven infants who had seizures. Plasma concentrations of TPM were lower in infants who were treated with MH and received phenobarbital than those treated with DH with or without concomitant phenobarbital and those treated with MH without phenobarbital, but the differences did not reach statistical significance (most newborns had plasma concentrations within the reference range [5–20 mg/L] for TPM, indicating that oral absorption of TPM is not affected by hypothermia).[12]

Among the nine infants in whom the TPM reached a virtual steady state, there were no statistically significant differences in the pharmacokinetic parameters between the DH and MH groups. However, the DH group did exhibit lower AUC_{0-24}, lower C_{avg}, and longer $T_{1/2}$. Additionally, neonates treated with both TPM and phenobarbital exhibited shorter $T_{1/2}$, maximal and average plasma concentrations, AUC_{0-24}, and oral clearance than infant treated with TPM alone. The only statistically significant difference between the infants treated with both phenobarbital and TPM and those treated with TPM was a lower C_{min} ($p = .032$) in the infants receiving both medications. The authors asserted that the lack of significant findings in most of the parameters was likely because of small sample size so no conclusions can be made from these results.[12]

The TPM dose of 5 mg/kg/day is the lowest dose among maintenance dosing schedules and was chosen because of the presumed potential for higher TPM plasma levels during hypothermia. In addition, the researchers chose once per day dosing because of presumed longer half-life of the drug during hypothermia. Filippi and associates reported that the plasma TPM concentration among the hypothermic infants in this study was higher than the levels found in the literature among normothermic infants receiving analog doses of TPM.[12] Among the infants in this study, one infant in the MH group had a plasma TPM concentration greater than 20 mg/L and three infants in the DH group had plasma TPM levels greater than 25 mg/L. Because there was no difference in plasma levels between those who received both TPM and phenobarbital and those who received TPM alone, the researchers suggested that it was the depth of hypothermia that accounted for the variability among the DH group. The researchers concluded that the dosing range in this study resulted in levels within the reference range for the drug for most infants during hypothermia; however, the optimal dosing TPM dosing schedule still needs to be established for neonates during therapeutic hypothermia.[12]

In 2011, Filippi and associates sought to determine the efficacy of phenobarbital for the treatment of seizures in neonates undergoing hypothermia for HIE.[13] Infants treated with hypothermia in this study had to meet the same criteria as described earlier. Nineteen infants with clinical seizures were included in the study. These infants were treated with a 20 mg/kg loading dose of phenobarbital. Additional doses of 5 mg/kg (up to a maximum total dose of 40 mg/kg) were given if seizures recurred. Phenobarbital was started at a mean age of 2.8 ± 1.6 hours. All of the infants were outborns and transferred into the study NICU for cooling. The first seven patients on phenobarbital received a planned maintenance dose of 2.5 mg/kg every 12 hours. These patients were the high-dose group. The remaining 12 patients received 1.5 mg/kg of phenobarbital every 12 hours. These infants were the low-dose group.[13]

Although 18 of the 19 infants had mean plasma phenobarbital levels within the reference range (10–40 mg/L), infants in the high-dose group had significantly higher plasma levels than those in the low-dose group beginning 48 hours after the dose. There was wide variability in the plasma levels in both groups; however, the levels in low-dose group were more consistently within reference range. One infant who received a total loading dose of 35 mg/kg had a plasma phenobarbital level greater than 40 mg/L.[13] There were no significant differences in the pharmacokinetic parameters between the high-dose and low-dose groups; however, there was a trend toward higher values for maximum plasma concentration, minimum plasma concentration, area under the curve from 0 to 72 hours and from 60 to 72 hours, and average plasma concentration among the infants in the high-dose group.

Maximum, minimum, and average plasma concentrations and half-life were higher among these hypothermic newborns than levels reported in the literature for normothermic newborns.[13] Based on these findings, it is important to monitor plasma phenobarbital levels in infants treated with therapeutic hypothermia for HIE, especially those infants who received doses of 40 mg/kg or more.[13] Gentamicin is routinely prescribed to treat presumptive infections in newborns—including those with HIE—in the NICU. Two potential adverse effects of gentamicin are nephrotoxicity related to total dose and ototoxicity related to high-peak levels.[14] In a retrospective chart review, the Lui and colleagues collected data from 55 newborns with HIE who meet criteria for the CoolCap trial in two NICUs in the United Kingdom. Infants were treated with 72 hours of either mild hypothermia (33–34.5°C; 30 infants) or normothermia (36.5–37.5°C; 25 infants). Average age at initiation of cooling was 4.5 hours. Each infant had received at least one dose of gentamicin 4–5 mg/kg/day (36 percent received 4 mg/kg/day; 64 percent received 5 mg/kg/day). Average age at the time of initial gentamicin dose was two hours. Gentamicin was delivered more than approximately 20 minutes. Frequency of dosing was adjusted based on plasma creatinine concentrations, urine output, and serum gentamicin concentrations. The initial serum gentamicin trough levels were drawn at an average age of 26 hours, prior to, but as close as possible to the second dose.[14]

The researchers found a close correlation between plasma creatinine concentrations and trough serum gentamicin concentrations regardless of treatment group ($r^2 = 36$). There also was no difference between groups for serum gentamicin concentrations, 2.19 ± 1.7 mg/L in the hypothermic group and 2.30 ± 2.0 mg/L in the normothermic group ($p = .73$). The authors reported that there was no significant difference in serum gentamicin concentration between the infants who received 4 mg/kg/day and 5 mg/kg/day. Forty percent of the troughs in both group were greater than the recommended trough concentration of less than or equal to 2 mg/L. There was a correlation between elevated serum gentamicin concentrations and high plasma creatinine concentrations or a urine output of less than 1 ml/kg/h. Correlation coefficients were not reported. The researchers concluded that impaired renal function related to an acute perinatal asphyxia event and as evidenced by elevated plasma creatinine concentrations is associated with elevated serum gentamicin concentrations. Therefore, serum gentamicin concentration monitoring is highly recommended in any infant experiencing an acute perinatal asphyxial event caused by the adverse renal consequences regardless of whether they are treated with therapeutic hypothermia.[14]

Róka and associates evaluated the effect of hypothermia on morphine pharmacokinetics.[15] Sixteen infants who were participating in a multinational study of moderate total body hypothermia (33–34°C) for HIE were enrolled in this morphine pharmacokinetic study as well. Ten of the infants were treated with hypothermia and six were treated using normothermia. Cooling was initiated before 6 hours of age and continued for 72 hours. All of the infants received a single loading dose of 50–150 mcg/kg morphine hydrochloride before six hours of age, followed by a continuous infusion of 5–30 mcg/kg/h. The infusion was adjusted based on physical signs and symptoms of discomfort. The infusion was discontinued after 72 hours or sooner if an infant was extubated or did not exhibit signs of distress. Venous samples for morphine concentration were collected at 6, 12, 24, 48, and 72 hours after birth.[15]

Both the hypothermia and the normothermia groups received similar cumulative morphine doses. Serum morphine concentrations were not available for one infant in the hypothermia group at 12 hours, for another infant in the hypothermia group at 48 hours, and for three infants in the hypothermia group at 72 hours. One infant in the hypothermia group was not started on a continuous morphine infusion until 24 hours. The morphine infusion for an infant in the normothermic group was stopped at 48 hours. A total of 70 samples was used to analyze serum morphine concentrations.[15]

The researchers found that serum morphine concentrations were higher in the infant treated with hypothermia. The median morphine concentrations from 24 to 72 hours after birth were 292 ng/mL (137–767 ng/mL) and 206 ng/mL (88–327 ng/mL) in the hypothermia group and normothermia group, respectively ($p = .014$). The mean AUC for serum morphine concentration over the entire assessment period was higher in the hypothermia group compared with the normothermia group. Serum morphine concentration reached steady state after 24 hours in the normothermic infants, but serum concentration continued to rise in the hypothermia group and never achieved a steady state. Because serum morphine concentration steady state was not reached among the hypothermia group, morphine clearance could not be calculated for this group. Using multiple regression analysis, the researchers determined that serum morphine concentrations were correlated with morphine infusion rate, cumulative dose, and hypothermia.[15]

The researchers concluded that because of the potential for morphine toxicity during hypothermia, clinicians should monitor drug levels should they decide to use morphine for sedation during induced hypothermia.[15]

CONCLUSIONS

This review of the recent literature addressing specific drug metabolism in neonates treated with therapeutic hypothermia summarizes data on only four of the many potential medications used to treat acutely ill neonates with HIE. Additionally, each of these studies was small; the largest study included only 55 infants and was retrospective.[14] The size of the studies could explain the lack of significance in many of the results. Until there is greater understanding of effect of hypothermia on the metabolism of drugs commonly prescribed in the NICU, it is important to monitor available drug levels in neonates treated with therapeutic hypothermia.

There is a clear need for larger retrospective studies on drug metabolism during hypothermia. Tortorici and associates' theoretical time course for CYP450 enzyme activity suggests decreased enzyme activity during cooling and returns to normal after rewarming.[3] Studies need to be expanded to provide specific age-related dosing normograms for the medications used in this population.[3]

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