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Procedural Pain Management for Neonates Using Nonpharmacological Strategies

Part 2: Mother-Driven Interventions

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ABSTRACT

This is the second of a 2-part series to provide an overview of our current level of knowledge related to nonpharmacological strategies to diminish the pain associated with commonly performed procedures in the NICU. In our first article we discussed the prevalence of repeated pain exposure in the NICU and the importance of nonpharmacological strategies specifically containment or facilitated tucking, swaddling, positioning, nonnutritive sucking, and sweet solutions. These strategies are generally nurse-driven and we believe their importance has been underutilized. In this article we will emphasize the importance of maternal presence as a mediator for pain relief. The efficacy of breastfeeding, maternal skin-to-skin care (often referred to as kangaroo care), and multisensorial stimulation such as auditory and olfactory recognition will be the primary focus of our discussion. In addition, although primarily mother-driven, these strategies are ultimately nurse-enabled, thus the importance of this connection cannot be under appreciated with respect to successful implementation in the NICU.

KEY WORDS: breastfeeding, maternal presence, NICU, neonates, nonpharmacological interventions, pain, preterm neonates, procedural pain, skin-to-skin contact

Globally, the term motherhood has been associated with the role of provider and comforter and the consequences of maternal-infant separation are well-known.¹⁻⁴ Yet, the world of neonatal care did not historically embrace this role and moth-

ers were often given little opportunity to touch or comfort their infants. Nevertheless, over the past 2 decades, an evolving paradigm shift embracing a family-centered care philosophy has impacted many aspects of neonatal care.⁵ In addition, there has been a rapidly growing interest in using mothers of preterm neonates as agents of growth promotion and comfort in the NICU setting.⁶ This has been based on 2 premises: the loss of comfort-providing role of parents in critical care settings and the positive effects of maternal touch, specifically skin-to-skin or Kangaroo Mother Care (KMC), on various parameters of neonatal stability and state regulation. In studies of parents of critically ill children and infants, parents were concerned about pain management, and found their child's suffering a primary source of stress.⁷⁻¹⁰ Even in situations where the staff believed that they were handling the child's pain well and the parents were not distressed, this was not the case from the parents' perspective.¹¹ In a US/UK study in 11 NICUs with 200 parents, almost all reported that

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their infant had experienced moderate to severe pain that was worse than they had expected.¹² Concerns about pain predicted the most variance of parental stress. Another major concern of parents is the loss of their parental role, including providing comfort, particularly for mothers.¹³⁻¹⁵ In the earlier study of NICU parents, 87% stated that they would wish to participate in managing their infant's pain.¹² In our studies of mothers engaged in skin-to-skin care while their infant underwent routine heel lance in the NICU, 80% of the mothers reported positive feelings and 99% said they would do it again.¹⁶ Similarly in our study of infants and toddlers in the pediatric intensive care unit where mothers used touching and distracting talking/singing to their child during a painful procedure such as chest tube removal, 84% reported positive feelings about being with their child during the painful procedure. All but 1 reported that they would do it again. One mother of a newborn summed the expressions of others, "I know I am the best person to comfort my baby and I am sure every mother feels that way."¹⁷ Fathers, in particular, feel left out of most of the care of their infants, but wish to be more involved, even if it is frightening.^{16,18}

While nonpharmacological interventions such as nonnutritive sucking and sucrose have been reported over a longer time,^{19,21} the interest in Kangaroo Care (KC) for pain is recent. Originating in Colombia in 1978, KMC, described as mother holding the baby naked with only a diaper in prone upright position against her bare breasts, was used to improve the survival of preterm babies in the context of scarce technological resources for neonatal care and it was first described by Rey & Martinez in 1983.²² Advantages for the infant are numerous: enhanced physiologic,^{23,24} state,²⁵ and temperature stability,²⁶⁻²⁸ improved regulation,²⁹ the establishment of exclusive breastfeeding,³⁰⁻³³ and even benefits in later development have been reported.^{34,25} Not surprisingly, KMC also promotes family bonding.³⁵⁻³⁸ Given that KC promotes autonomic stability and state regulation and that it promotes bonding between the mother and the infant, it was logical that it would be tested as an intervention for pain where the response to noxious stimuli include autonomic arousal and crying in the infant as well as maternal associated stress. While the duration of providing KC ranges from continuous around-the-clock holding (KMC) as an alternative to incubator to shorter intermittent periods, normally referred to as skin-to-skin contact (SSC), we will focus on its use for pain with shorter times.

In our first article we provided a review of the prevalence and adverse effects of repeated pain exposure in the NICU and the importance of non-pharmacological strategies specifically containment or facilitated tucking, swaddling, positioning, nonnutritive sucking, and sweet solutions. These strategies are generally nurse driven and we believe their importance has been underutilized. In this article we

will emphasize the importance of maternal presence as a mediator for pain relief. The efficacy of breastfeeding, maternal skin-to-skin care, and multisensorial stimulation such as auditory and olfactory recognition will be the primary focus of our discussion. Although primarily mother-driven, these strategies are ultimately nurse-enabled, thus the importance of this connection cannot be under appreciated with respect to successful implementation in the NICU.

BREASTMILK/BREASTFEEDING

Breastmilk or Breastfeeding Versus Placebo

The possible benefits of supplemental breastmilk and or breastfeeding in full-term and older newborns have been tested in several studies. In a systematic review of 11 clinical trials, breastmilk and breastfeeding were shown to provide analgesia during routine procedural pain from heel stick and venepuncture.³⁹ Neonates given supplemental breast milk via syringe or pacifier had significantly less increase in the heart rate and behavioral pain scores compared to the placebo group. However duration of crying time and oxygen saturation change when compared to placebo group were not statistically significant. Composite pain measured using the Premature Infant Pain Profile (PIPP) scoring system were significantly different between the breastfeeding group and the placebo group (weighted mean difference: -6 [range: -7 to -4]), but these scores were not so different when compared with the glucose plus pacifier group (weighted mean difference: 1.30 [range: 0.05-2.56]).³⁹ In the one study to use the Douleur Aigue du Nouveau-Né, pain scores were significantly lower in full-term infants (N = 200) randomized to breastfeeding (mean = 2.65; SD = 2.31) during heel stick for metabolic screening when compared with infants in the control arm (pacifier in mothers arms) (mean = 5.15; SD = 2.0).⁴⁰ The Douleur Aigue du Nouveau-Né score between breastfeeding group and glucose group was not statistically significantly different (MD: -0.8; 95% CI: -2.0 to 0.5).

Breastmilk Versus Sweet Taste

Supplemental breastmilk alone in the absence of breastfeeding does not appear to be as analgesic as sweet taste. Infants receiving breast milk had significantly higher increase in heart rate changes (MD = 14; 95% CI = 4-23) compared with those given 25% sucrose⁴¹ or 30% glucose (MD = 7; 95% CI = 1-13).⁴² Only one study has examined breastmilk analgesia in infants younger than term gestation. Skogsdal⁴² examined 128 late preterm infants divided equally between 4 groups (no intervention, 1 mL 30% glucose, 1 mL 10% glucose and 1 mL breastmilk) with a mean (SD) gestational age at birth of 35.5 (2.3) and postnatal age of 5.4 (4.9) days undergoing a heel stick. Cry duration was 75% lower in the 30% glucose

group (0-90 seconds) compared with control (0-270 seconds; $P < .01$), while both the 10% glucose and breastmilk lowered crying duration by 50% that was not reported as reaching statistical significance.

Conversely, breastfeeding has been shown to be as effective as sucrose for the relief of procedural pain.⁴⁰ Shorter crying times (seconds) were reported in both the breastfeeding (28.62 ± 33.71) and sucrose (9.56 ± 12.96) groups when compared with the control (103.50 ± 63.69). The mean oxygen saturation levels of the sucrose group were significantly higher than the control group, but no difference was observed between sucrose and breastfeeding groups.

One study has reported that breastfeeding may be superior to sucrose.⁴³ Following random assignment, 101 healthy term infants at least 60 hours old undergoing heel lance for metabolic screening had lower median PIPP scores in the breastfeeding group (3.0) when compared with the infants receiving 1 mL sucrose solution (8.5). In addition, physiological parameters and cry duration were significantly improved while breastfeeding. The median heart rate increase, oxygen saturation decrease, and duration of first cry for the breastfeeding group were, respectively, 13.0, -1, and 3 and for sucrose group were 22, -3, and 21. The heart rate increase (13 versus 22, $P < .005$) and oxygen saturation decrease (-1 versus -3, $P < .001$) that normally accompany this procedure were significantly lower in the breastfeeding group as compared with the sucrose group.

Breastfeeding in Combination With Sweet Taste

Little research has been conducted examining the potential cumulative benefit of sweet taste and breastfeeding when provided simultaneously. In the one study that has, Gradin⁴⁴ compared the effectiveness of breastfeeding, or 1 mL glucose alone, and in combination, with controls receiving no interventions, on 120 full-term infant's pain response during venepuncture. When compared to controls, both breastfeeding prior to the venepuncture and prior breastfeeding in combination with glucose diminished cry duration in seconds (combination = 18; breastfeeding = 63; glucose = 93; control = 142). Median PIPP scores were lowest in the combination group 7 versus 9 (glucose), 10 (breastfeeding), and 11 (control) groups.

Breastfeeding and Older Infants

Breastfeeding has been shown to be effective in relieving pain response for older infants up to 6 months undergoing vaccinations in outpatient settings. Healthy 2- to 4-month-old infants ($N = 64$) returning to a clinic for their second-, third-, or fourth-month immunization with intramuscular diphtheria, tetanus, and pertussis were randomized to be breast-fed before, during, and after the injection or to be given the injection according to routine clinic procedure (no breast-

feeding).⁴⁵ The crying time duration was shorter in the experimental (breastfeeding) group (35.85 seconds) than in the control group (76.24 seconds; $P < .001$). Similarly, slightly older infants up to 6 months of age had reduced crying time (median [range] 20.0 seconds [0-120] vs 150.0 [0-180] $P < .001$) and reduced pain scores (Neonatal Infant Pain scores) (median [range] 3.0 [0-6] vs 6.0 [0-7] $P < .001$) in the breastfeeding group compared to those not breast fed during immunization.⁴⁶ No significant differences in heart rate and oxygen saturation levels were found between groups.

Summary

Overall, although exposure to breastmilk or breastfeeding, when compared with no intervention, has shown to diminish infant pain response to minor procedural pain, breastfeeding is significantly more effective than breastmilk alone. Maternal presence, which is necessary for breastfeeding, is the most likely factor mediating this difference. When compared to sweet taste, breastfeeding is at least as effective and may actually be more analgesic. A cumulative effect has also been shown.

KANGAROO MOTHER CARE/ SKIN-TO-SKIN CARE

Skin-to-Skin Care Compared to No Intervention in Full-Term Infants

The earliest study to examine the effects of SSC on pain response was conducted a decade ago in Boston.⁴⁷ Thirty full-term infants randomly assigned to 10 to 15 minutes of SSC prior and during to heel stick had reduced crying by 82% and grimacing by 65% compared with infants who received standard care (swaddled in crib). Significant differences remained in the 3-minute recovery period. Elevation in heart rate was smaller in the SSC group (8-10 vs 36-38). Similarly, 10 minutes of SSC effectively reduced behavioral pain response in healthy full-term newborns less than 2 hours old undergoing intramuscular Vitamin K injection.⁴⁸ Cumulative Neonatal Infant Pain scores measured immediately following the injection were significantly lower ($P < .001$) in the SSC group compared with controls. Pain scores greater than 3 representative of moderate to severe pain were recorded 98% of the time in the control infants compared to 38% for SSC. Mean duration of crying was also longer, 24.61 in the control group versus 14.55 seconds in the SSC group.

Skin-to-Skin Care Compared to No Intervention in Preterm Infants

The first study to examine the effects of SSC on preterm infants between 32 and 36 weeks gestational age undergoing heel stick was conducted in 2003⁴⁹ and other studies followed. These studies consistently show that SSC significantly reduced PIPP scores

during and after the painful procedure. A 2-point reduction was found at 30, 60, and 90 seconds after heel lance in one study⁴⁹ and at 90 seconds ($P < .001$) in another study with very preterm infants.⁵⁰ An even larger difference was found by Akcan, Yigit, and Atici⁵¹ at 1, 2, and 3 minutes after heel lance or venepuncture (mean of 7.0, 4, and 4 in the SSC group and mean of 15, $P < .001$, 15.5, $P = .001$ and 15, $P = .047$ in the control group).

The effect on facial actions is also clear. Significant lower scores were found in the Neonatal Facial Coding System at heel lance (difference = -1.140, $P = .023$) and heel squeezing (difference = -1.872, $P < .001$).⁵² Crying length during the lance and after the lance was less in infants in SSC than in controls ($P = .003$ during and $P = .02$ after)⁵³ and in another study it was 55 seconds versus 96.2 seconds during heel lance ($P < .001$) and 5.8 versus 25.5 during recovery ($P < .01$).⁵⁴ The mean duration of cry was reduced by 37.4% in infants after 15 minutes in SSC (mean = 2.5 minutes) compared with infants swaddled in the crib (mean = 4.8 minutes, $P = .024$).⁵² As in studies of other interventions the effect on heart rate did not always reach statistical significance in spite of a lower mean in the SSC group.⁵² However, in very preterm infants in SSC, average heart rate was significantly lower at 30, 60, and 90 seconds post-heel lance and average oxygen saturation levels were significantly higher at 60 and 90 seconds post-heel lance compared with infants in the incubator.⁵⁰ In this trial the time for heart rate to return to baseline after the end of the procedure was shorter, 123 seconds (95% CI = 103-142) for the SSC condition and 193 seconds for the incubator condition (95% CI = 158-227) ($F = 13.6$, $P < .0000$) showing that in the context of stress caused by pain SSC contributes to energy conservation and homeostasis maintenance which are of major importance for preterm infants' growth and development. This hypothesis was supported in a recent study examining the effect of SSC on autonomic stability during heel lance in very preterm infants (30-32 weeks).⁵⁵ Heart rate variability was significantly more stable in infants in the SSC condition compared with infants in the incubator. Low frequency variability was higher in SSC at baseline ($P < .01$) and at heel lance ($P < .001$), and high frequency variability was higher in SSC condition than in the incubator condition ($P < .05$). The low frequency/high frequency ratio remained more constant during SSC compared to the incubator condition and was significantly lower during recovery in SSC ($P < .001$) demonstrating a more mature regulatory state.⁵⁵

MULTISENSORY STIMULATION

It remains unclear whether the comforting effect associated with SSC is derived solely from the direct skin contact that occurs between a mother and her newborn or if it is simply one aspect of a combination

of multiple sensory inputs comprising auditory and olfactory recognition.

Auditory Recognition

There is now compelling evidence that the human fetus by 29 weeks gestational age is capable of auditory perception⁵⁶ and has the ability to learn and remember auditory stimuli from their intrauterine environment. This early experience may have lasting effects on the developing brain and later self-regulation.⁵⁷ Infants as young as 3 days recognize their mothers' voice and heartbeat^{58,59} and this memory has been shown to affect physiological and behavioral responses and have soothing effects.⁶⁰ When exposed to voices, near-term fetuses' had an increased heart rate⁶¹ and more robust vagal tone⁶² in response to the mother's voice and a decrease in response to a stranger's voice. In addition, infants between 33 and 41 weeks gestational age were even able to distinguish language (English vs Mandarin) following recorded playing of passages in 1 or the other language, further supporting early auditory attention and memory facility.⁶³ These findings were not supported in a recent study examining the soothing effect of maternal voice in preterm infants during heel stick procedure.⁶⁴ A limitation of the study was the high volume of the recorded sound (70 dB), which may have contributed to the negative findings. Numerous studies have determined that maternal heartbeat and recorded voice or lullaby can be soothing to both full-term and preterm newborns. Following birth, infants exhibited heart rate decelerations, increased nonnutritive sucking, more relaxed facial expressions, diminished crying and less body movements when hearing syllables that are paired with the maternal voice than when syllables are paired with another woman's voice or silence.⁶⁵ Exposure to familiar sounds has been positively associated with improved physiological stability (decreased heart and respiratory rate and an increase in oxygen saturations),⁶⁶ less agitation⁶⁷ and more time in stable sleep or quiet alert state.⁶⁸ Maternal heartbeat has also been shown to blunt the effects of pain associated with a tissue breaking procedure in a study in which 131 full-term infants underwent a heel stick while being exposed to either maternal heart rate, Japanese drum with identical rhythm, or no sound. Infants exposed to maternal heartbeat had reduced facial response and crying, and lower levels of cortisol and dehydroepiandrosterone following heel stick when compared to the other 2 groups.⁶⁰ In a crossover design study with infants 30 to 41 weeks gestational age, music therapy alone consisting of intrauterine maternal pulse sounds with soothing music, music therapy combined with nonnutritive sucking, nonnutritive sucking alone and no intervention were compared when used for 5 minutes after heel lance.⁶⁸ Music therapy alone had the strongest effect on neonates' heart rate and the effect lasted after the intervention was

withdrawn. Nonnutritive sucking with music therapy had the strongest effect on neonates' TcPaO₂ levels and pain behavior. Butt & Kisilevsky,⁶⁹ in a randomized crossover design, exposed 16 preterm neonates to vocal or instrumental music for 10 minutes after the end of a heel lance. During this period, infants above 31 weeks had a significantly more rapid return of heart rate, behavioral state, and facial expressions of pain to baseline levels in the presence of music compared with the absence of music.

A recent review included 9 randomized trials that examined the efficacy of music for procedural pain management (circumcision and heel lance) in both full-term and preterm infants. Although the authors concluded that music therapy might improve physiological stability and diminish pain response during procedural pain, due to the poor quality of some of the studies and large variation in reported outcomes, more rigorous trials were needed to confirm this findings.⁷⁰

Olfactory/Aromatherapy Recognition

Maternal related olfactory stimuli have been associated with comfort and diminished pain response in both term and preterm infants.⁷¹⁻⁷⁴ These findings support the hypothesis that infants remember, recognize, and prefer smell that is associated with their prenatal environment. In 2 studies examining full-term infants, regardless of being formula fed,⁷⁵ or breastfed,⁷⁶ infants consistently turned toward familiar amniotic smell. Similarly, infants exposed to maternal odor had increased sucking bursts⁷⁴ and cried significantly less⁷³ compared with those exposed to no odor.

Newborns also appear to have early learning and memory of olfactory stimuli and that this memory can affect both behavioral and hormonal response to a tissue breaking procedure.^{71,72,77} To determine the effect of familiar, unfamiliar, or no odor on infant pain response during heel stick, 44 breast-fed newborns were randomly assigned to 1 of 4 groups: group 1 was naturally familiarized with their mother's milk odor, group 2 was familiarized with a vanilla smell, and groups 3 and 4 did not receive any familiarization. During and after the heel stick, group 1 was presented with their familiar mother's milk odor, group 2 was presented with the familiar vanilla, group 3 was presented with an unfamiliar odor, and group 4 was a control group. Results revealed that infants who smelled a familiar odor (their mother's milk or vanilla) cried and grimaced significantly less during the recovery phase compared with those infants exposed to a nonfamiliar or no odor condition. Infants exposed to their mother's milk also exhibited significantly less motor agitation during and after the heel stick.⁷⁷ Similar findings were also seen in additional studies in which full-term⁷² and preterm (average 32.3 weeks gestational age)⁷¹ infants exposed to a familiar vanilla smell during heel stick had significantly less crying and grimacing compared

with infants exposed to an unfamiliar odor. These studies provide compelling evidence that all newborns have the capability to remember familiar sound and smell and this ability can provide comfort and modulate pain response.

Mechanisms of Nonpharmacological Interventions

There are likely several mechanisms underlying the specific pain-relieving effect of each of these maternal driven nonpharmacological interventions. One hypothesis, that could be related to all of them, is derived from the Gate Control Theory proposed by Melzack and Wall.⁷⁸ Accordingly, stimuli traveling ascending pathways inhibit the nociceptive signals from painful stimuli through various endogenous mechanisms located along the spino-thalamic tract.⁷⁹ The stronger these competing stimuli are, including multiple modalities, the more effective they are in blocking the perception of pain. This helps explain why multiple modalities such as kangaroo care, breastfeeding, or sensorial saturation, which involve tactile, auditory, and olfactory mechanisms are more effective than single modalities such as olfactory or auditory.

Another mechanism, at higher levels of the brain is the release of endorphins.⁸⁰ Endorphins are released both by stress (including pain) as well as positive stimuli such as touch.^{81,82} The mechanisms underlying the comforting effects of breastfeeding⁸³ and maternal and familiarized smell remain unknown although it too has been theorized to act via the activation of endogenous opioid pathways and are almost certainly multisensory. Evidence for this hypothesis is derived from both animal^{84,85} and human literature.⁸⁶ Other possible mechanisms, such as oxytocin increases in breastfeeding and kangaroo care⁸² or state regulation in developmental care⁸⁷ have also been postulated.

Implications for Future Research

Although breastfeeding is targeted to late preterm and full-term infants and considered to be less appropriate for those born very preterm, SSC is effective in very preterm infants as young as 28 weeks. Both breastfeeding and SSC has been consistently associated with a reduction on behavioral pain response and improvement in physiological stability. This latter effect may also have implications for other neonatal outcomes such as the incidence of bronchopulmonary dysplasia and retinopathy of prematurity that have been associated with frequent increases or fluctuations in oxygen supplementation. The examination of benefits of these strategies for sicker infants and those requiring assisted ventilation is a logical next step.

It remains unclear whether the benefit of SSC is unique to a mother or whether others such as fathers, unrelated women, or siblings could provide similar comfort. In addition, current studies have been limited

to 1 pain exposure. Whether mother-driven strategies remain efficacious over time has yet to be determined.

The impact of KC goes beyond benefit to the infant, but also to the mother-infant dyad. Two trials have also shown that mothers who were assigned to engage in KC with their preterm babies showed more bonding behaviors^{25,35,36} and expressions of bonding sentiments.³⁸ Interestingly for this proposal in Feldman's matched control study,²⁵ even fathers' sensitivity and responsiveness to neonatal cues were better in the maternal KC group at 3 months corrected age and there was more affectionate touch between parents to the infant and to each other.³⁶ There has been 1 prior study that examined maternal cortisol levels in mothers during KC.⁸⁸ In that study mothers cortisol levels, heart rate, self report of mood, and stress were measured pre-post KC at the first and fourth time of doing KC. Mood increased and the other parameters decreased both pre-post KC as well as between the first and fourth KC session. Further studies examining the effect on parental stress and bonding is warranted.

Finally, more research is needed to facilitate the successful implementation of these mother-driven strategies into the normal routine of the NICU. Increased unit flexibility regarding the timing of nonurgent blood collection and parent visiting, ergonomics, and safety issues for staff are a few of the areas that have been identified for future study.

CONCLUSION

In conclusion, given the efficacy of numerous non-pharmacological interventions⁸⁹ for procedural pain in neonates and the difficulties with pharmacological agents in this population, for common painful procedures such as heel lance and venepuncture, nonpharmacological interventions should be the first choice in uncompromised infants. They are cost-effective and easy to administer. Mothers are clearly implicated in breastfeeding and kangaroo care, but can also be included in other interventions.^{90,91} Initially, there is a requirement to train staff and parents on these methods, and it may seem easier to give a solution in an intravenous line than to coordinate care to coincide with parental visiting. Nevertheless, parents find pain the most distressing aspect of the NICU and also wish to actively participate in comforting their infant.¹³ These approaches are consistent with modern family-centered care in neonatal units in which the best interests of the infant and family are put ahead of staff convenience.

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