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REVIEW ARTICLE

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Neonatal pain: A journey spanning three decades

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Abstract

From 1980 into present day, 2020, the evolution of neonatal pain research is told as a journey by one researcher, Celeste Johnston. At the beginning of her work, there was essentially no interest or work in the area. She was fortunate to be led into the area by a clinical problem: how to determine the amount of pain babies in the NICU were experiencing. That question resulted in over three decades of work with neonates. Measuring pain was the first challenge and is one that remains a focus of current research. Initially, the only choices for treating pain in neonates were either opioids or anesthetics, each with problems. Research on sweet taste and more recently on skin-to-skin contact has offered effective and safe options for procedural pain. Although progress has been made in the incidence of pain management in infants, it still is far less than it could be. Steps along the way of measurement, treatment, and knowledge utilization are chronicled by this researcher.

KEYWORDS

animal models of pain, measurement of pain, neonates, non-pharmacological management of pain, pain

1 | BACKGROUND

The time this story starts is early in the 1980s. When looking back, it now seems astonishing that in that era almost no attention was given to pain in neonates. There were no measures, no interventions other than opiates, which were rarely used, no policies on neonatal pain management, and prevailing myths that infants either did not feel pain or that it was short lived. I had begun working at the Montreal Children's Hospital when finishing my doctorate in counseling psychology in 1979. For my dissertation, I studied the effect of peer models as teachers. When I first went to the Children's, I started work on using peer models for preoperative anxiety in children aged four and older. It became clear early on, that if the pain was controlled, the anxiety was less. This is so obvious in hindsight! I had worked in an adult burn unit after my Masters degree in nursing where, being appalled at the pain burn patients suffered, I started attending pain rounds in the early days of Ron Melzack's clinical work. I considered that I therefore knew something about pain! I started connecting with different disciplines at the Children's in an attempt to have better management of pain in young patients, but my early focus was on verbal children.

At some point, in the mid 1980s, I was approached by nurses in the NICU to help with a problem they had regarding palliative care babies. Judi Collinge was the former Head Nurse and remained on the unit as a Research Nurse, and she and I had worked together to form a nursing research group at the Children's[1] so she was my conduit into the NICU, bearing in mind that I had no clinical expertise in that population. The nurses' dilemma was that they perceived babies in palliative care were in pain and nothing was being done for it. They wanted to know how they could prove to the medical staff that the babies were suffering. Could I help them?

2 | MEASURING PAIN IN NONVERBAL PATIENTS

In searching the literature for measurements of pain in infants, there was nothing published. It was a tabula rasa. In discussions with colleagues, I did discover that in studies of facial expression or cries, pain had been one condition that had been examined. As I was working on a grant submission, unbeknownst to me, Owens and Todt were conducting research on a description of newborn pain response. Their paper was published in Pain in 1984,[2] and my grant was funded in 1985. The Owen and Todt study examined duration of crying and heart rate as parameters, but they had recommended more parameters be used. Happily my application had included 4 parameters including heart rate, crying duration as well as spectrograph analysis, facial expression, and body movement. We published that as a preliminary study.[3]

A "pain cry signature" was what I was hoping to find in the next study, along with examining developmental changes over the first year of life. My sample consisted of healthy infants 2, 4, 6, and 12 months of age coming for routine immunization. There were three conditions in which we measured their response, anger with held head so they could not turn surprise with jack-in-the-box, and pain from the immunization. The pain was always last as they would have been too upset for the other conditions. There were several problems with that study. The two-month-olds were totally unsurprised by the jack-in-the-box, and very few infants cried in all three conditions, although enough to analyze. There was a pain cry which was high pitched, long in duration, and dysphonated, which is heard as harsh.[4,5]

However, I had wandered from the initial request about infants in the NICU, the ones undergoing numerous painful procedures, as opposed to healthy infants receiving an injection every two months. Two things became apparent in my multi-dimensional approach. First of all, sick preterm neonates tend not to have the energy to cry and are often intubated, and secondly, they are (hopefully) bundled, so that you cannot see body movements. So, I decided to refocus on that population.

At the time, I was most fortunate to have Bonnie Stevens as my first PhD student. I must say that it was with her arrival that my productivity increased dramatically. Having bright, productive students is something all researchers should strive toward!

I was able to obtain funding again to study pain in infants, this time, in the NICU. Bonnie and I shared the data from the cohort of infants from 32- to 36-week gestational age. In this study, we exposed infants to a sham heel lance in which heel was warmed and wiped with alcohol, and a cotton-tipped swab is applied to the heel; then, the heel is squeezed, and motion made as though applying an adhesive dressing. The real heel lance was compared to the sham heel lance in a cross-over design on different days. Bonnie used data from the heel lance condition for her work,[6-8] and I looked at the different response to conditions as well as the change over time. I was also very fortunate at that time to work with Ken Craig and Ruth Grunau in examining approaches to pain measurement.[9,10] I had to confess that data were suggesting that facial expression, not cry, was a more discriminative parameter of the pain response. Ken suggested that the cry was a signal, like a siren to gain caregivers attention, and facial expression communicate what state the infant was in Ref. 11.

Bonnie and I worked with our data and developed the premature infant pain profile[12] which she has since tested multiple times so that it now has become a standard of pain measurement. She also tested it in older infants and for its clinical utility. It has undergone one revision to account for very young infants who may not show a response to pain.[13] There are a couple of unique things about the PIPP that account for the success of it. First of all, it incorporates two factors of gestational age and behavioral state at the time of the procedure, both of which impact pain response. Secondly, not widely known, the cutoff points for scoring were derived from actual data from over 100 infants, which showed a quadrimodal distribution, accounting for scoring on the PIPP of 0, 1, 2, and 3. That is, the scoring was not chosen arbitrarily, but empirically.

We noticed that some infants showed absolutely no response to a tissue-damaging procedure, and we wondered whether there were factors that could account for that. We examine a data set from a control condition of 120 infants. We examined age, Apgar score at 5 minutes, severity of illness, sex, race, wake/sleep state, previous study sessions, total number of painful procedures since birth, and time since last painful procedure in a logistic regression. Younger age, both gestational and postnatal, sleep state, and shorter time since last procedure predicted no response.[14] Other studies had reported on age and state, but none had examined time since last procedure.

Although my major population was with preterm neonates, yet another bright PhD student, Manon Ranger, looked at infants in the pediatric intensive care unit (PICU) undergoing painful procedures. She used a new method, certainly new for pain in infants, to gain some glimpse of sensory cortical activity in response to pain, near-infrared spectroscopy (NIRS).[15] NIRS is noninvasive and can access activity of the infant cerebral cortex through cerebral bloodflow calculations of oxygenated vs nonoxygenated hemaglobin. Thus, the amount of activity in the somatosensory cortex of the infant can be determined and has been shown to be sensitive to noxious stimuli in infants.[16]

3 | PAIN MANAGEMENT PRACTICE

Although there were studies emerging that suggested there were important consequences to unmanaged pain (more detail below), it seemed as though there was still little being done for babies in pain, particularly for minor, but frequent procedures. Along with Judi Collinge and neonatologist, Jack Aranda, we conducted a study across Canada with 14 NICU's to examine pain management practices.[17] Shockingly, less than 1% of procedures were given medication for painful procedures. This was before nonpharmacological studies had demonstrated efficacy. Twelve years later, I conducted a follow-up survey across 14 NICU's in Canada, not all the same as the first survey, and found that practice had improved with approximately

half of all procedures being treated, all but 15% with nonpharmacological methods including sucrose which by that time had been demonstrated to be efficacious for a single procedure.[18] One finding that particularly interested me was that a factor predicting whether or not interventions were used was when the parent was present, their being there increasing the likelihood of management.

Another bright PhD student working with me, Margot Latimer, studied factors predicting pain management practice among NICU nurses. While expecting that multiple admissions during a shift or nurses education level and such factors to explain variation, she found that the leadership in the unit was predictive.[19] The more collegial and less hierarchical the nurse-physician relationship, the higher the degree of pain management practice by the nurses.

4 | CONSEQUENCES OF UNTREATED PAIN

In the late 1980s, Sunny Anand published two seminal papers that unequivocally showed that untreated pain in neonates undergoing surgery resulted in major hormonal and metabolic stress responses that contributed to increased morbidity and even mortality.[20,21] These studies, along with baby Jeffrey Lawson, who died following cardiac surgery with no anesthesia or analgesia, and whose mother, Jill Lawson, published widely her baby's completely unethical ordeal, brought the treatment of pain into the public and policy maker domain. There was newfound interest in the topic with such bodies as the American Academy of Pediatrics publishing statements about treating pain in infants.

While profound, Sunny's studies and baby Jeffrey Lawsons needless tragic death, they did not address the daily pain that nonsurgical patients in the NICU were experiencing. Maria Fitzgerald started her pivotal series of studies demonstrating the long-term consequences of minor procedures in infants and, perhaps more importantly, showed the developmental vulnerabilities of the preterm neonate.[22-24]

I decided to examine the effect of being in the NICU over 4 weeks.[25] I recruited two groups of infants, both 32-week gestational age; however, one group was four days postnatal age (younger) and the other group was four weeks postnatal age. We examined the pain response and regressed factors including gestational age at birth, 5-minute Apgars, birthweight, severity of illness, and number of painful procedures on the pain parameters of the PIPP. The older infants had a higher physiological response, that is, higher heart rate, lower oxygen saturation levels, but lower facial action expression. So, we were able to document clear changes in response over time including inability to appropriately mount a physiological response and to robustly communicate state through facial actions.

Recognizing the difficulty that I had with conducting human studies that clearly showed brain changes, this being before brain imaging studies on infants, I embarked on some animal studies with my brilliant colleague, Dominique Walker, a developmental neurobiologist. While on sabbatical in 2000, I spent time in her laboratory, her rat nursery, to learn some of the techniques used in animal models and to actually participate in the design as well as the conduction of a study to examine long-term consequences of pain. We were particularly interested in pain sensitivity following repeated neonatal pain, mimicking experience in NICU's. In our design, we had three groups of newborn rat pups. One group was never disturbed from the nest, and another group was simply removed from the nest and dam for 15 minutes four times daily. The third group was removed and given a pawprick with a 26 g needle and replaced in next 15 minutes later. We included the simply separated group as earlier studies had not controlled for maternal separation. We tested at ages equivalent to adolescence, adulthood, and senior age on thermal sensitivity and inflammatory pain response. There was no difference in inflammatory pain response but the separated only group had lower thresholds than the pain group, which we could not explain. When we reviewed the videotapes and counted maternal grooming behaviors when the pups were returned to the nest, we discovered that the pain group received one and a quarter times more grooming than the separated only group. When this was factored in, the pain group had a lower threshold, as has been predicted.[26-28] This led to an "ah-ha" moment, which I will elaborate on later in the next section.

We followed up these studies by examining the influence of maternal grooming on pain response[29,30] and continued to note that there was a blunting effect on long-term responses with maternal influences.

5 | PROCEDURAL PAIN MANAGEMENT

We were becoming aware of the hazards of using opiates with preterm neonates[31] and were searching for alternatives. Topical anesthetics were a group of drugs to explore, Eutectic Mixture of Local Anesthetics (EMLA) cream being one of promise.[32-34] We had used it ourselves in a study on circumcision.[35] Along with Bonnie Stevens and two neonatologists/pharmacologist, we were funded to study its use for heel lance pain management. Somewhat to our surprise, but EMLA was not effective.[36] A group is Sweden reported that EMLA did not have an opportunity to bind in thin infant skin.[37,38]

We were also aware of the blunting of pain response with sweet taste in both animals and full terms.[39,40] We then focused on sucrose. I did a few studies on sucrose, examining timing and dosage,[41] and comparing to other interventions such as rocking.[42] With Bonnie Stevens as principal investigator, we investigated the addition of sucrose to other developmentally sensitive interventions such as prone position or pacifier.[43] All of these studies and of others had studied sweet taste, predominantly sucrose, for a single event. Since it was showing to be highly effective, it was being used more and more in NICU's. However, I was concerned about its continued analgesic effect as well as whether or not it would mitigate long-term consequences of repeated pain. We conducted a study of 107 newly born infants who were less than 31 weeks gestational age who would receive 1% sucrose or placebo for every painful procedure in the first week of life. Our primary outcome was three parameters of

the Neurobehavioral Assessment of Preterm Infants (NAPI), namely motor development and vigor, alertness, and orientation at 32-, 36-, and 40-week gestational age. We fully expected the infants receiving sucrose to do better, but not only was there no difference between groups, when examining the sucrose group, the greater the number of doses, the lower the developmental scores.[44] This was the first study to indicate that sucrose was not the unequivocal answer to procedural pain.

Since sucrose was a mainstay of procedural management of pain, and some studies had found no problem with it, we decided to do a secondary analysis on the data set to see if there was a threshold of doses, below which the developmental scores were within the norms. We found that infants who received less than 10 doses of 0.1 mL 24% sucrose per week were within 2 SD of normed means of the NAPI.[45]

Marilyn Aita, another bright PhD student, studied the effect of environmental noise and light on pain response. She had worked in a NICU and had particular interest in Developmental Care, which is based on decreasing environmental stimuli stressors, among other practices. In her study, infants were outfitted with masks and earmuffs to blunt these extraneous stimuli, since the layout of the NICU did not allow for randomization with or without stimuli. The outcomes were indices of physiological stability, primarily heart rate variability. Unfortunately, the masks and earmuffs were distressing to the infants, so that other means of reducing light and noise need to be found.[46]

6 | ITS ALL ABOUT THE MOTHER

Above, I mentioned the "ah-ha" moment in our animal study when we realized that maternal grooming blunted the effects of pain. I also mentioned above that pain management was more likely to be given to an infant if the mother was there. I had anecdotally noted that babies' oxygen saturation level increased and their heart rates decreased when a parent was beside the incubator touching them. I tried to study that by having a mat on the floor beside the incubator that had a sensor to turn on camera and capture not only behavior but heart rate and oxygen saturation level. The person stepping on the mat was to identify themselves as nurse, doctor, etc or mother, father. The machinery would also turn on for 30 seconds every 5 minutes when no one was there in order to have baseline data. Unfortunately, this study failed utterly in that nurses were straddling the mat to avoid being recorded!

I had also heard about Kangaroo Care, or more technically, skin-to-skin care as an alternative to incubators for preterm neonates in resource-poor countries.[47,48] Putting together my observations of the rat pups and their mothers as well as knowing of Kangaroo Care, I submitted for funding to study its effect. Just as I received word of success of funding, a study was published with full-term infants undergoing injection that showed its efficacy.[49] Our first study was with infants 32-36 weeks of age, as we thought younger infants may not have endogenous mechanisms developed enough to be invoked by Kangaroo Care. We found that it was efficacious.[50] We then decided to study it with younger infants, that is, 28-32 weeks and were happy to find that it was also efficacious in this group.[51] At this point, we had decided to no longer have no treatment control group as there were enough data for either sucrose or kangaroo care that it was unethical to withhold.[52] We then conducted studies on comparing kangaroo care to enhanced kangaroo care, in which the mother rocked, talked or sang to the baby, and offered her finger for the infant to suck. There was no difference between the conditions.[53] In some instances, mothers were not able to be present, so we started to examine other types of kangaroo care, even just using the mothers recorded voice, which was not efficacious,[54] possibly because the recorded voice was too loud, which we had set to be above ambient noise, which says something about the ambient noise. We noted that at times, fathers or grandmothers would volunteer to do Kangaroo Care when the mother was not available. We then embarked on studies of fathers compared to mothers and mothers compared to other women, not related to them, since grandmothers and maternal aunts share some characteristics such as scent and voice. In both instances, the mothers were more effective than others.[55,56] As mentioned above, we did not have a no treatment control group, but the pain scores from historical controls were much higher than either fathers or nonrelated women.

While conducting these studies, yet again I was fortunate to have a bright PhD student, Marsha Campbell-Yeo who studied the effect of being cobedded with the twin in multiple births. Since these babies had been together since conception, often sharing the same amniotic sac, touching each other, we wondered whether continued care with the twin would be comforting. Using the standard of care, sucrose, as the control, we compared pain response in twins who were or were not cobedded. The pain scores were not different between the two groups of twins, but the time to recovery was less in the cobedded group[57] as was the cortisol response.[58]

Again in consideration of clinical conditions in which infants might be too young or unstable to go into Kangaroo Care, I looked for other possibilities. For very tiny infants, who are disturbed by cutaneous stimulation of any type, I decided to study Therapeutic Touch, in which direct physical touch does not happen, but rather energy fields are accessed by the therapist. The study was conducted in such a way that if we had positive results, there could be no source of bias: A site in Sweden allocated condition and only the Therapeutic Touch nurse had access to the code, and she either conducted Therapeutic Touch or stood by the incubator doing math calculations in her head with the curtains pulled around her. There were two cameras: one focused on the baby's face for coding and one on the nurse for validation of the procedure (which were never viewed), and heart rate and oxygen saturations were obtained through clinical monitors. There were absolutely no differences between the groups.[59] The plots could have been superimposed. I remain skeptical about the effect of Therapeutic Touch, although people I highly respect are proponents of it.

Given our studies and the number of other studies on Kangaroo Care for pain that were coming out, we decided to do a Cochrane review on Kangaroo Care for procedural pain. We wrote one review[60] revised it[61] and are currently (year 2020) revising it to include newer studies. It is clear that it is effective as a means of preventing response from procedural pain in both behavioral and, somewhat less, physiological parameters.

We were also wanting to determine whether Kangaroo Care remained efficacious over time, whether it was as good as the standard of care, sucrose, and whether there were longer term developmental differences. We compared three randomized groups in three heel lances spread across the entire NICU stay: 24% sucrose alone, Kangaroo Care alone, or the combination of sucrose and Kangaroo Care. There were no differences in pain responses nor in developmental outcomes.[62] We concluded that since Kangaroo Care alone was as efficacious as the standard of care, and the addition of sucrose did not improve on any outcomes, that it should become the standard of care. We are continuing to analyze that database to examine amount of time in Kangaroo Care and even effects on epigenetics of hormones.

7 | FUTURE DIRECTIONS

Being this far in my career, I am often asked to comment on future directions for research on pain in neonates. In actual fact, I cannot predict the future and trust that my younger colleagues will continue to work on it so as to alleviate suffering in our tiny patients. The few comments I do have are more general.

In terms of the quest to measure pain and not another state, I am not certain that such a thing is possible, because I am not certain that pain is a differentiated sensation in humans of any age, especially those with immature sensory processing mechanisms. If you consider that in the adult literature, there has been an ongoing search for some way to differentiate chronic pain from depression, but more recently, there is an acknowledgment that not only do the co-exist, they might be the same. Similarly, for neonates, any high level stimulation, be it noise or light or pain, will cause distress which may be painful.

The effect of the mother is only recently being appreciated. We need only look at other mammals to see the profound comforting effect mothers have. Our recent studies of maternal (or other caring persons) comfort using ventral skin-to-skin contact is only the beginning of ways in which mothers and other caretakers can be more involved in reducing pain. The study on maternal voice that I conducted which had negative results should be repeated with appropriate sound levels. Maternal scent should be further explored. Basically, parents need to be more involved in caring for their preterm neonates. With acute observations, ideas might emerge for study.

Finally, the best knowledge is useless unless it is implemented into care. Much work is now being conducted on evidence-based care. I applaud and encourage people engaged in that work because that is the ultimate goal of the knowledge generation.

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There are far too many people who have helped me in my journey in studying pain in neonates for me to list. I have mentioned a few (Sunny Anand, Ken Craig, Ruth Grunau, Dominique Walker, Jack Aranda) and a few of my students who were working directly on my program of research, Bonnie Stevens, Marsha Campbell-Yeo, and Manon Ranger. I am so delighted that their stellar careers are taking the work I started far beyond what I could have: Marsha following multiple avenues of the effect of the mother on pain response and Manon on both using animal models to test effects not possible in humans and to use brain imaging to study pain. Bonnie Stevens has continued work on sucrose analgesia and has made giant steps to improve pain management by clinical staff. I am confident that the journey will continue to improve the lives of infants who would be having pain.

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