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Current Controversies Regarding Pain Assessment in Neonates

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Although over 40 methods of pain assessment in infants are available for use in clinical practice, unrecognized and under-treated pain remains one of the most commonly reported problems within the Neonatal Intensive Care Units. A number of factors have been found to account for differences in the robustness of the pain response in neonates of varying gestational ages. Discrepancies between behavioral and physiological pain indicators have also been reported. With newer technologies, there is an opportunity not only to verify infant pain perception, but these tools may allow an identification of which of the observed indicators are most sensitive in particular clinical situations. The current controversies regarding pain assessment in preterm and term infants are reviewed to define the most important issues and to develop a dialogue for future directions.
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Although tremendous progress has been made over the past two decades, there remains a worldwide issue to be resolved regarding how we can recognize and respond to neonatal pain. Since the seminal work by Anand and coworkers[1] in the 1980s demonstrating the preventive effect of fentanyl on the surgical stress response of preterm babies, important advances have occurred in the study of pain within this population. It is now commonly acknowledged that infants feel pain and communicate their experience through a variety of cues. Even though more then 40 pain assessment tools are available, no single instrument has demonstrated superiority over the others for use across varied painful conditions or clinical situations. Thus, no specific measure has been set as the "gold standard" for pain assessment of infants in research and clinical practice.[2] In addition, nearly all of these instruments have been developed to measure acute procedural and/or short-term pain (postoperative), leaving the assessment of prolonged/recurrent pain often experienced by the critically ill preterm and term neonates still unresolved.[3] As such, under-recognition and under-treatment of pain in infants still persists.

During hospitalization in a neonatal intensive care unit (NICU), infants undergo a range of 2 to 14 invasive procedures each day, for which less than one-third receive an analgesic therapy.[4,5] Additionally, the younger these babies are in gestational age, the more painful procedures they will undergo. Although the ascending pathways conducting nociception may develop by the 20th week of gestation, descending pathways that play a role in the inhibition of incoming pain impulses do not mature until the last trimester, which increases the preterm infant's sensitivity to pain.[6-8] Thus, the cumulative effects of these painful experiences added to the multiple sources of stress in the NICU could have significant negative consequences on the neurodevelopment of these vulnerable neonates.[9,10]

Anand and Craig[11] exposed several weaknesses of the widely accepted definition of pain from the International Association for the Study of Pain (IASP) and suggested that the ongoing progress in pain research should allow for a revised version of the definition of pain. As such, they proposed that the required self-report inherent within the definition of pain could have consequently led to the failure of acknowledging and properly treating pain in infants and young children. In response to this problem, they suggested that the "behavioral alterations caused by pain are the infantile forms of self-report and should not be discounted as 'surrogate' measures of pain."[11] Health care professionals need to learn how to identify these cues and pay special attention to the neonate's

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unique way of communicating pain to fulfill their mandate of providing pain relief and comfort. In addition to the difficult task of identifying and decoding the infantile form of self-report is the fact that the nature of these behavioral indicators will vary within each developmental stage of the infant's life as well as between different gestational ages.[11,12] Furthermore, aside from the obvious immediate reactive distress signals to acute pain, such as facial expressions and cry, the muted reactions to ongoing pain are more subtle and have been regarded as a shutdown of activity comparable to behaviors associated with depression.[3] Recognizing these less noticeable indicators can be particularly challenging for caregivers.

This review of the questions and controversies regarding pain assessment in preterm and term infants is proposed as a "springboard" for future research and clinical applications. It is anticipated that the specification of the precise issues will help to focus efforts to address these concerns.

Physiological Versus Behavioral Responses to Pain

Most of the available pediatric pain assessment instruments are multidimensional incorporating both behavioral (facial action, body movement, cry) and physiological (heart rate, respiratory rate, blood pressure, oxygen saturation) indicators. Dissociation between these two classes of measures has been reported with an average correlation of a mere 0.3,[13-15] whereas within these two classes, the associations are stronger. Behavioral measures, especially facial actions, are more likely to respond selectively to pain,[16] whereas physiological indicators change in response to painful stimuli, but they also change for numerous other reasons and are not specific to pain.[14,17,18] This makes interpretation difficult. For example, in a study of sucrose and simulated rocking, the facial actions showed large differences between the conditions favoring sucrose, whereas the heart rate showed smaller differences and in the opposite direction.[19]

Recently, Stevens and others examined the factor structure of 19 pain indicators, both physiological and behavioral, in a sample of 149 infants undergoing an acute painful event.[20] Facial actions accounted for a greater proportion of the variance (close to 40%) with oxygen saturation, heart rate, cry, and heart rate variability accounting for lesser, but important, contributions of 8% to 26% of the additional explained variance.

As many physiological cues and some behavioral cues, such as crying, are not specific to pain, researchers and clinicians are faced with the difficult task of discriminating between these to decide whether these are truly indicative of pain and not of other similarly manifested states, such as agitation, distress, anxiety, stress, or hunger.

In an effort to address this, Barr proposed that the concept of "honest signaling" might be relevant to the "pain signaling" issues that clinicians face on a day-to-day basis.[13] The origins of this model are derived from Darwin's theories of evolutionary biology. According to this model, certain "signals," or physical features or behavioral traits, served the purpose of attracting sexual partners, such as bright colors or rich plumage, but had the detriment of also attracting predators. Consequently, only the best "fit" signals could escape this "cost." Barr hypothesized that this theory could be applied to infants displaying certain signals as a way of eliciting attention and care from their environment.[13] Thus, certain behaviors associated with pain, such as facial grimacing, could be qualified as "signals" rather than clinical signs of pain and could explain the dissociation between behavioral and physiological responses seen in this population.

In extremely fragile neonates, crying involves several "costs" to their health status, such as high energy consumption or increased intracranial pressure, which could lead to serious adverse consequences. Unfortunately these "weaker" signalers often need the most attention and are at greater risk from the adverse effects of untreated pain, which further challenges caregivers in critical care settings. Barr[13] categorized most physiological reactions as being "*covert*" signals in contrast to their behavioral responses, qualified as "overt" in nature. This would be consistent with the facial actions being more sensitive; that is, caregivers can observe the face, but heart rate is not readily observable. The idea of signaling was supported by Craig's proposal that the baby's cry acts as a siren to attract the caregivers' attention, and once the attention has been obtained, the facial actions convey the state, such as pain, to the caregiver.[21] These arguments are easily understood in the context of healthy infants undergoing an acute painful event, but are not completely applicable to critically ill or compromised infants, given the energy costs of mounting a robust pain response.

As discussed below, a number of factors were found to account for differences in the robustness of the pain response.[12,15,18,22-24]

Age and Pain Expression

When assessing pain in preterm neonates, clinicians need to consider age. Age significantly affects the robustness of pain behaviors, both postnatal age at the time of observation and gestational age (GA) at birth.[15,16,18] Because infants as young as 25 to 26 weeks GA clearly demonstrate reactions to pain,[18,25] it is of utmost importance that we consider age when evaluating pain responses in this population. Infants born at greater gestational ages have remained in the protective uterine environment further into their development and have more robust responses to acute painful procedures (heel lance) than infants born earlier in gestation but who have spent the same developmental time in NICU.[12] When 120 preterm newborns with an average age of 28 weeks GA were subjected to heel lance procedures, 20% of their study sample showed no response.[18] The odds that these preterm babies would demonstrate changes in their behavioral and physiological pain indicators were 0.94 times greater per week of postconceptional (PCA) at birth and 0.66 times greater per week of postnatal age.

One persistent controversy is whether the lack of response reflects reduced pain perception or the infants' inability to respond. The pain signaling system appears early in life, probably well before late gestation.[26] Thus, the former explanation is unlikely. Babies instinctively communicate their pain experience to their environment via behavioral and physiological cues in an effort to obtain aid and relief. After repeated unanswered attempts at communicating pain, these vulnerable infants could possibly, as a defense mechanism and energy-restoring system, learn to become helpless. On the other hand, this lack of expression could be seen as a sign of simple exhaustion.[18]

State, Experience, and Pain Expression

The neurobehavioural state of preterm and full-term neonates before a painful event may alter their responsiveness to pain. Several studies reported that infants in an awake state before acute pain displayed more robust behavioral and physiological reactivity when compared with those in quiet sleep states.[18,22-24] Similarly, preterm neonates who were sleeping had 18-fold odds of demonstrating dampened responses to pain in comparison to awake infants.[18]

For infants with the same GA but different postnatal ages, the factor most predictive of dampened facial actions was the number of painful procedures that the infant had undergone while in the NICU, even while controlling for risk factors such as Apgar scores and birth weight.[12] Recently, Grunau and coworkers[27] showed that, although prior exposure to pain did not predict the heart rate variability in extremely low gestational age (ELGA) and very low gestational age (VLGA) babies, it did have an effect on facial responses in the ELGA neonates. In fact, after controlling for severity of illness, the more skin-breaking procedures these infants had endured, the less robust were their facial expressions, consistent with the earlier study.

Not only does greater procedural pain exposure alter their behavioral reactivity to subsequent pain in neonates,[12] but the time since the last painful procedure also affects this response. The odds of blunting a preterm infant's pain indicators were 0.96 times greater for a 30-minute difference between painful procedures.[18]

In summary, behavioral and physiological markers have been found to be discrepant and vary according to different factors. Although we cannot act on innate factors, such as GA, postnatal age, or the wake/sleep state of preterm and term neonates, we can intervene for other predictor variables altering their pain responses, such as the number of procedures performed or the timing between procedures.

Assessment of Prolonged Versus Acute Pain

As stated earlier, signs of prolonged or ongoing pain in infancy tend to be more subtle and qualitatively different from acute pain, leading to under-recognition and under-treatment of pain. When the pain related to skin-breaking procedures evolves into more prolonged types of pain, preterm infants hospitalized in the NICU have limited energy reserves and, thus, may not have the ability to maintain the psychophysiological activity involved in the acute pain response.[2,28] Furthermore, despite the prevalence of recurrent or chronic conditions and ongoing postoperative pain in this population, identification and evaluation of signs indicating "chronic" pain remain to be more thoroughly studied. To this date, only three assessment tools have been developed for prolonged pain: the EDIN (Échelle Douleur Inconfort Nouveau-Né),[29] the N-PASS (Neonatal Pain and Discomfort Scale),[30] and the DEGR (Douleur Enfant Gustave Roussy Scale), the last for older children.[31] Basic psychometric testing, such as construct validity for two of these tools (N-PASS and EDIN) and validation for use in preterm infants for the DEGR[2] have not been performed.

Recently, Holsti and coworkers[32] reported the construct validity of a newly developed unidimensional behavioral pain assessment tool for preterm neonates: the Behavioral Indicators of Infant Pain (BIIP). The BIIP includes two hand actions which show promising results as possibly being, in addition to facial reactions, selective behavioral cues signaling pain.

This area of research is mushrooming because of ongoing concerns for the long-term and possibly permanent effects of pain on the immature brain.[33-35] Although pain experiences in the newborn period are not consciously accessible to the individual, the plasticity of supraspinal foci involved in sensory processing supports the evidence that recurrent pain in infancy alters the behavioral responses to pain in adulthood.[33] It is imperative, therefore, that pain in early life be treated adequately to prevent this cascade of events. To guide the safe and appropriate use of pharmacological therapy, accurate, reliable, and valid pain assessments are essential.

Flexion Reflexes for Procedural Pain

Andrews and coworkers[36,37] set out to test spinal cord sensory processing in neonates with and without chronic conditions using flexion withdrawal reflex thresholds. Von Frey filaments were used to evoke abdominal skin reflexes (ASR) in groups of infants with or without prenatally diagnosed unilateral hydronephrosis. On the side ipsilateral to the hydronephrosis, 70% patients showed significantly lower ASR thresholds than the contralateral side. ASR reflex thresholds increased and reflex radiation (as hip flexion) decreased from 30 to 95 weeks PCA in the control group, but this developmental trend did not occur in the hydronephrosis group, even on the unaffected side of the abdomen.[36]

In postsurgical subjects, Andrews and Fitzgerald[37] reported that the ASR threshold decreased by up to 78% following surgery, associated with an increase in reflex radiation. ASR thresholds remained below preoperative values for 24 hours on the operated side. In addition, if the infants were operated for a chronic condition, lower ASR thresholds existed even before surgery. These authors proposed that sensory processing modifications (hypersensitivity) induced by abdominal surgery and visceral pathology could be quantitatively and reliably assessed with the ASR technique.[37] Although these findings are promising, such methods are not clinically applicable because of questions around the clinical utility of the ASR method. Moreover, how can we equate these reflex reactions with pain perception? The ASR may simply reflect hyperexcitability of the spinal pain pathways, which would at best represent an indirect measure of ongoing pain.[2] Reflex foot withdrawals induced by Von Frey filaments were not associated with cortical activity,[25] so that the changes in ASR threshold may simply indicate activity in the peripheral nerves, dorsal root ganglia, and the spinal cord, without traveling up to supraspinal processing areas, where pain is "perceived."

Cortical Activations

Many of these assessment issues might be surmounted in the near future as the ability to have a window into the infant brain and measure pain perception progresses.[2] Promising results have been reported on using noninvasive electroencephalography and neuroimaging techniques to measure somatosensory and frontal cortex activation. Recent studies in premature infants indicated that painful stimuli cause circulatory and metabolic changes in specific cortical and subcortical regions.[25,38] Near Infrared Spectroscopy (NIRS) detects subtle changes in oxygenation and de-oxygenation of the hemoglobin in the brain. Recently, it has been demonstrated with NIRS that cortical activation occurs in response to painful stimuli in newborns.[25,38]

Bartocci and coworkers[38] demonstrated specific somatosensory cortical activation after venipuncture in 40 preterm neonates born at 28 to 36 weeks of gestation and postnatal age 25 to 46 hours. Bilateral and symmetrical somatosensory areas were recorded in 29 neonates, and the contralateral somatosensory and occipital areas were recorded in 11 infants. Increases in oxygenated hemoglobin in somatosensory areas in both groups occurred after skin disinfection (tactile stimulus) and venipuncture (painful stimulus) but not in the occipital cortex. Differing areas of blood flow indicate a specific response to painful stimulation in the brain. Interesting additional findings showed that somatosensory responses to painful stimulation measured with NIRS were more prominent on the left side of the cortex, of higher intensity in male subjects, directly associated with postnatal age, and inversely correlated with gestational age. These two later results corroborate earlier cited observations of blunted behavioral cues of pain in extremely premature infants.[38]

Exciting work by Slater and coworkers[25] also demonstrated somatosensory cortical activation after heel sticks in preterm and term neonates. In a sample of 18 neonates studied 1 to 5 times at 25 to 46 weeks GA, painful stimulation caused a significant increase in oxygenated hemoglobin in the contralateral somatosensory cortex and was independent of global hemodynamic changes. These responses also depended on the GA and awake/sleep states of the infants, with less robust contralateral cortical responses in younger neonates than older ones, or neonates asleep than awake. Even babies as young as 25 weeks GA displayed a significant response after heel stick. Interestingly, a Von Frey stimulation of the plantar surface of the foot causing a flexion withdrawal response did *not* lead to a cortical activation. Spinally mediated reflex withdrawal responses in limbs after the occurrence of a painful procedure were higher in intensity and duration in the youngest neonates and dampened with age.[39,40] Thus, these findings underline the fact that spinal and cortical nociceptive processing operates through distinct mechanisms.[25]

Fernandez and coworkers[41] measured electroencephalographic response to a noxious stimulus in two groups (sucrose versus water) of term newborns to determine whether sucrose would change their cortical responses. In reaction to heel stick, both groups of infants showed physiological changes with increased heart rate, but relative right frontal EEG activation was demonstrated only in the neonates who received water. Thus, sucrose seems to reduce the "negative" cortical activation in response to aversive stimulation in neonates. Although these findings show great potential for future research, the clinical use of these methods is limited by movement artifact.[41]

It would thus appear that there is a new avenue in pain assessment practices to undertake with populations such as premature and/or critically ill infants that may be more sensitive and specific to higher level pain processing. Furthermore, these methods could be used as a way of confirming the validity of available or new pain assessment instruments.

New Standards in Pain Measurement

Pain assessment, considered as the fifth vital sign, is part of basic care and must be thoroughly evaluated. The consensus statement for the prevention and management of pain in newborns developed by the *International Evidence-Based Group for Neonatal Pain* advises individualized care plans for pain assessment which take into consideration many clinical and contextual factors for each patient.[42] Health care professionals are urged to use standardized pain assessment tools with tested reliability, validity, clinical utility, sensitivity, and specificity to differing GAs and types of pain (eg, acute, recurrent, or chronic pain; procedural, postoperative, inflammatory, or neuropathic pain). Concomitantly, health care providers must take into account environmental, contextual, and timing factors in their assessment. As such, no single pain assessment instrument includes the entire array of indicators, which entails that NICU staff must be trained to use several pain tools. Is this applicable at the bedside? With respect to current clinical realities (understaffing, high turnover of staff, number of extremely sick neonates increasing, budget cuts, etc.), we must search for ways to best assure knowledge transfer from research to practice.

Recently, Pasero and McCaffery[43] brought to light the difficulties of assessing pain when self-report cannot be obtained and the need to revise policies and procedures to make sure that pain is well treated. Instead of using *"pain-behavior" scales* that are only useful at confirming the presence of pain in certain critically ill patients and which provide a "pain-behavior score, not a pain-intensity rating," these authors proposed a *Pain-Assessment Protocol for Patients Who Cannot Self-Report*. Within this six-item *Protocol*, they recommend to avoid establishing ward-based policies that entail the use of a particular pain-behavior scale for all nonverbal patients; each patient is different and, thus, the suitability of a measurement tool must be verified patient by patient. The absence of research demonstrating equivalencies or correlations between self-reported pain intensity ratings and specific behavioral-observation scores for a number of behaviors, in any patient population, limits this approach.[43]

Future Directions

The study of neonatal pain measurement has been prolific over the past two decades. Several of these methods involve assessment of pain responses to acute procedural pain and, more recently, prolonged or recurrent pain. Only a few standardized assessment tools, all for acute procedural pain, have undergone thorough psychometric testing. Neonates with neurological impairment may have altered pain processing and modulation, and although their responses appear to be similar,[20,44] clinical staff believe that they respond differently.[45] Given the growing interest in the mechanisms involved in the maturation of higher cortical functions in the preterm and term neonates, it is probable that future directions in pain research will focus on brain involvement, both as a site for measurement as well as examining effect of pain on brain structure and function.

Meanwhile, the controversies that continue to plague those caring for infants in pain include dissociated response systems, lack of observable responses due to depleted energy sources, the effect of specific factors on the pain response, and a shift from acute to ongoing or chronic pain. Bedside noninvasive neuroimaging with NIRS, EEG, or other technologies are showing promising results in their usefulness to detect cortical activation related to painful events. Further studies are necessary to determine the utility, feasibility, and clinical significance of novel assessment instruments during differing painful situations, including ongoing pain, and within varying populations. Determining the best approaches to allow the smooth transmission of research findings to the clinical bedside remains an important issue to tackle. Although over 40 measures of infant pain have been published, except for literature in the past 3 years, considerable overlap occurs in the indicators reported. Newer technologies will not only verify infant pain perception, but may also allow the identification of the most accurate or sensitive observed indicators in specific situations. Large samples coming from multiple centers will allow robust analyses of the range of painful conditions as well as individual variability. Although much progress has been made for pain assessment in neonates, the newer techniques offer great promise for resolving the controversies discussed here.

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