Pain Assessment and Measurement in Neonates

An Updated Review

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ABSTRACT

Pain assessment and measurement are the cornerstones of pain management. Pain assessment connotes a comprehensive multidimensional description. Conversely, pain measurement provides a numeric quantitative description of each factor illustrating pain qualities. Pain scales provide a composite score used to guide practice and research. The type of infant pain instrument chosen is a significant factor in guiding pain management practice. The purpose of this review was to summarize current infant pain measures by introducing a conceptual framework for pain measurement. Although more than 40 infant pain instruments exist, many were devised solely for research purposes; several of the newly developed instruments largely overlap with existing instruments. Integration of pain management into daily practice remains problematic. Understanding how each instrument measures infant pain allows clinicians to make better decisions about what instrument to use with which infant and in what circumstances. In addition, novel new measurement techniques need further testing.

Key Words: assessment and measurement, infant, neonates, pain, pain tools and instruments

In the past several decades, scientific discovery related to neonatal pain during early infancy has dramatically increased. An impressive body of neuroanatomical, neurochemical, and biobehavioral evidence shows that the fetus and newborns possess the ability to detect, perceive, and respond to painful stimuli.[1] Findings support that neonates may have a pain threshold that is 30% to 50% lower than that of adults and a lower pain tolerance than older children,[2,3] because of immature descending inhibition functions in higher-level nervous centers. The lack of descending inhibition, which is an important endogenous analgesic system that may "dampen" the pain inputs, explains how infant pain responses are often more profound than in the adult. Premature infants are even more hypersensitive to nociceptive stimuli than full-term infants because immature sensory processing and inhibition controls lead to lower thresholds for excitation and sensitization, thereby potentially maximizing the central effects of tissue-damaging inputs.[4,5] The younger, more premature infants are most sensitive to pain experiences and are likely to be exposed to an increased number of pain experiences because their stays in the neonatal intensive care unit (NICU) are longer than those of less premature infants.[5] As the fifth vital sign, pain needs to be monitored routinely in the clinical practice[6]; however, assessing infant pain continues to be an enormous challenge to neonatal care providers because these infants cannot speak and advocate for themselves when they experience pain, which is the gold standard for pain measurement in other age groups. Pain is personal; each person experiences pain differently, and this is also true for infants. The developmental factors related to differences in pain sensitivity and other contextual factors,[7] such as pain exposure, health status, behavioral

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status, and therapeutic interventions, make infant pain assessment even more complicated.

Pain assessment and measurement are the cornerstones of pain management. Pain assessment connotes a more comprehensive and multidimensional concept, and pain measurement intends to provide a numeric or quantitative description of the attribute of pain using a selected pain scale such that composite scores provide direction for intervention. Choosing valid and reliable instruments, as well as proven parameters for measurement in research, ensures the objectivity and quality of the data. In clinical practice, the appropriate interventions depend on accurate assessment and measurement. Although the scientific bases for neonatal pain are growing exponentially, treatment decisions related to infant pain continue to be debated and influenced by many factors. The outcome measures used to indicate and interpret neonatal pain are some of the most significant factors for guiding practice. The purpose of this review was to summarize and evaluate current pain measures in both preterm and full-term newborns by introducing a conceptual framework for the measurement of pain. Implications of pain assessment tools for practice and recommendations for further research are discussed.

CONCEPTUAL FRAMEWORK FOR MEASUREMENT OF NEONATAL PAIN

Pain is a challenging concept whether in caring for an adult or in a child. *Pain* has been defined by McCaffrey[8] as "whatever the experiencing person says it is and existing whenever the person says it does." The International Association for the Study of Pain (IASP)[9] defines *pain* as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." These definitions preclude infants because the requirement for subjective reporting of pain. Even though the IASP has updated the definition of pain in the notes[10] to clarify that "the inability to communicate verbally does not negate the possibility that an individual is experiencing pain," and Anand and Craig[11] offer an alternative perspective that pain in infants is an inherent quality of life that appears early in ontogeny to serve as a signaling system for tissue damage, the measurement of neonatal pain is highly dependent on the observer's judgment, and the indicators in the signaling system must be subjectively observed and determined by others. A conceptual framework (Figure) has been developed by the authors to illustrate influences of contextual factors, pain attributes, characteristics of pain stimuli, and characteristics of the observers for detection and measuring neonatal pain. This framework highlights the multidimensional aspects of pain assessment and provides clinicians and researchers guidance for pain management in preterm and full-term infants. Further support for our framework is provided in our discussion of pain measurement.

Neonatal Pain Attributes and Responses

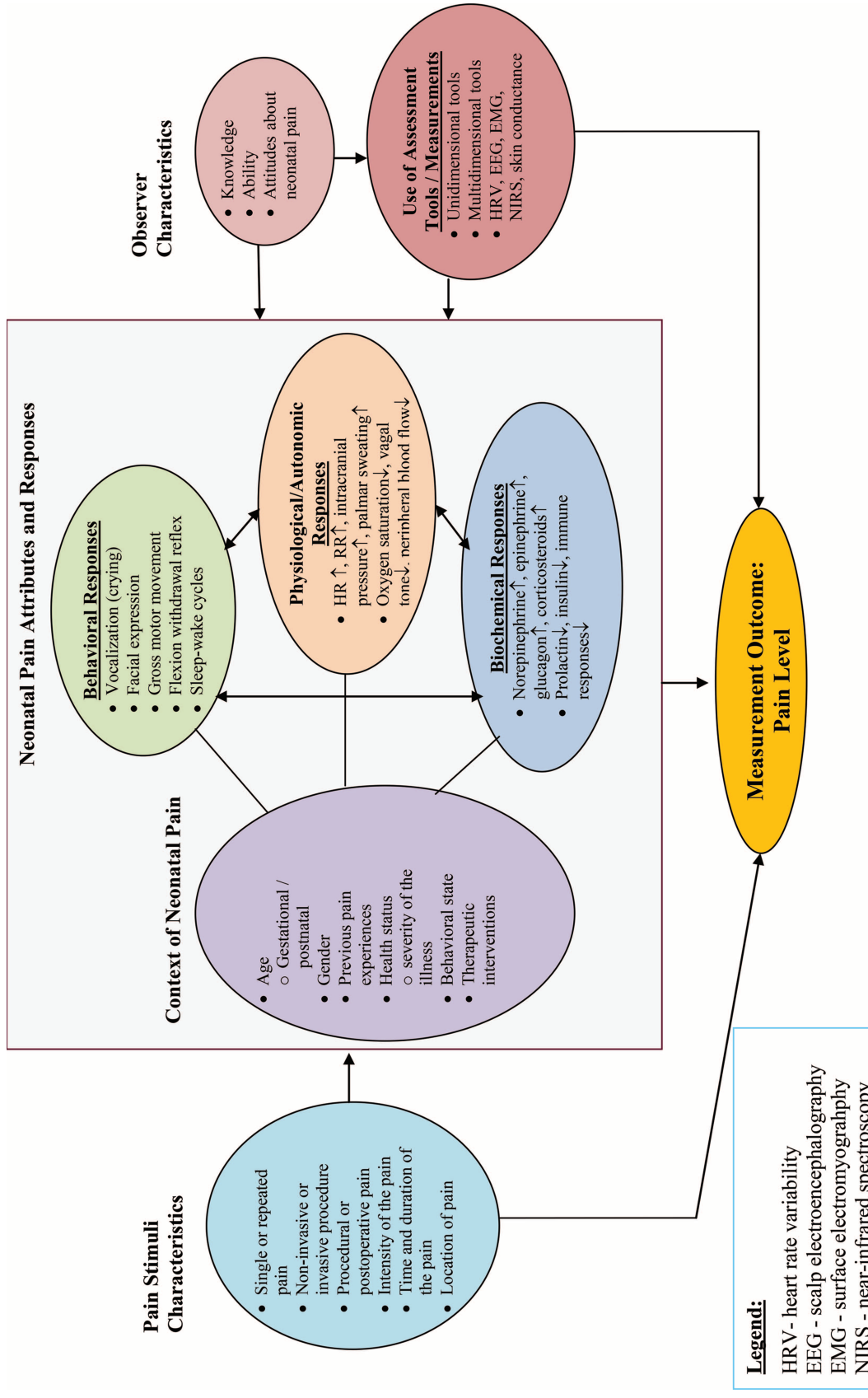
What evidence is needed to identify the attributes of a neonate in pain? How do we know an infant is in pain? Responses to pain in the neonate are associated with changes in behavior, physiology, and metabolism, and pain assessment can be made through gathering information from each of these 3 classifications of pain responses and indicators.

Behavioral Pain Responses

Expression of pain through behavior is the major means by which infants communicate their pain to care providers. Facial expression in response to procedural pain has been widely studied and shown to be different from responses to other tactile stimuli such as cleaning the heel or changing diapers.[12] Facial activity has been considered the most reliable and consistent indicator of pain out of all the unidimensional approaches across situations for both full-term and preterm infants.[13–16] Facial expressions include facial grimacing, brows bulged and furrowed, eye squeezed, nasolabial furrowing, lips opened and pursed, cupped tongue, quivering chin, and agitation.[17,18] The majority of the pain assessment tools (see Tables 1 and 2) use facial activity as one of the major pain indicators.

Crying is a common response to pain in infants and is considered to be another one of the most sensitive measures of pain.[19–25] *Cry* can be described in terms of its presence or absence of the time perspective, that is, latency to cry and duration of cry, and the amplitude and pitch—that is, high or low—and measured as fundamental frequency.[26] Infant pain cries have been shown to be spectrographically distinct in terms of frequency and pitch compared with cries caused by other stimuli such as hunger, anger or fear, and fussiness.[27–29] Changes in the patterns of neonatal cries have also been correlated with the intensity of pain experienced during circumcision and can be accurately differentiated by adult listeners.[30] Some preterm and acutely ill infants may not audibly cry during heel sticks and other painful procedures due to depleted energy reserves or may be unable to cry because of the presence of an endotracheal tube.[31] In addition, because as many as 20% of premature infants do not cry during and after heel stick,[31] inaudible crying, often called "silent cry" when the infant forms a "cry face," is considered a valuable measure in addition to audible crying for infant pain assessment. Audible and inaudible crying responses to heel stick pain have been successfully tested in experimental studies examining the effects of kangaroo care[32] and sucrose on reducing infant pain.[33] Further studies using a psychoacoustic

FIGURE.



Conceptual framework of pain measurement in neonates.

TABLE 1. Unidimensional Infant Pain Measures

Instrument	Items	Age Group	Reliability and Validity	Clinical Utility
Designed for measurement of acute/procedural pain				
MAX: Maximally Discriminative Facial Coding System; Izard (1979)[141]	3 items: Forehead and brow, eyes and nose bridge, mouth	Full-term 1-19 mos	Inter-RR: 0.83 Content and construct validity: Yes CV: 0.87	Used to identify 10 emotions, including pain
NFCS: Neonatal Facial Coding System; Grunau et al (1987)[142]	9 items: Brow bulge, eye squeeze, naso-labial furrow, open lips, stretch mouth (vertical), stretch mouth (horizontal), lip purse, taut tongue, chin quiver	Preterm Full-term	Inter-RR: 0.88 Intra-RR: 0.83 Face, content, and construct validity: Yes CV: 0.89	Procedural pain Feasibility: Yes
IBCS: Infant Body Coding System; Craig et al (1993)[35]	5 items: Movements of hand and foot, arms, legs, head, and torso	Preterm Full-term 25-41 wks GA	Inter-RR: 0.83 Face, content validity: Yes	Procedural pain More sensitive in full-term infants
DAN: Douleur Aiguë du Nouveau-né; Carbajal et al (1997)[143]	3 items: Facial expression, limb movements, and vocal expression	Preterm Full-term 25-41 wks GA	Internal consistency: 0.88 Inter-rater agreement: Krippendorff R test of 91.2	Procedural pain
BIIP: Behavioral Indicator of Infant Pain; Holsti et al (2007)[34]	8 items: Behavioral state, 5 facial expressions, 2 hand actions (finger splayed, fisting)	Preterm 24-32 wks GA	Inter-RR: 0.80-0.92 Internal consistency: 0.82 Correlation with NIPS: 0.64	Procedural pain
Designed for measurement of postoperative pain				
CSS: Clinical Scoring System; Attia et al (1987)[144,145]	10 items: Sleep, facial expressions, cry, motor activity, spontaneous excitability, flexion of fingers and toes, sucking, evaluation of tone, consolability, sociability	Neonates and < 7 mos infants	Inter-RR: 0.79-0.88 Constructive validity: Yes Discriminant validity: Yes	Postoperative pain
LIDS: Livepool Infant Distress Scale Horgan et al (1996)[146]	8 items: Spontaneous movements, excitability, flexion of fingers and toes, tone, facial expression, quantity of crying, quality of crying, sleep pattern	Full-term	Inter-RR: 0.74-0.88 Intra-RR: 0.81-0.96 Content validity: Yes	Postoperative pain Distress

(*continues*)

TABLE 1. Unidimensional Infant Pain Measures (*Continued*)

Instrument	Items	Age Group	Reliability and Validity	Clinical Utility
FLACC: Merkel et al (1997)[147]	5 items: Face, legs, activity, cry, consolability	Preverbal/nonverbal children < 7 y	Inter-RR: 0.94 Content and construct validity: Yes	Postoperative pain
UWCH: University of Wisconsin Children's Hospital Pain Scale; Soetenga et al (1999)[148]	5 items: Vocal/cry, facial expression, behavioral/consolability, body movement/posture, sleep	Preverbal children < 3 y	Inter-RR: 0.92 Internal consistency: 0.93 Content, construct, and criterion validity: Yes	Postoperative pain Procedural pain
CHIPPS: Children's and Infant's Postoperative Pain Scale; Buttner et al (2000)[149]	5 items: Crying, facial expression, posture of the trunk, posture of the legs, motor restlessness	Newborns and young children	Inter-RR: 0.93 Internal consistency: 0.96 Content and construct validity: Yes Specificity and sensitivity: Yes	Postoperative pain
Designed for measurement of prolonged pain				
BPS: Behavioral Pain Score; Pokela (1994)[87]	6 items: Sleep, facial expressions, spontaneous motor activity, movements and rigidity of the limbs and body, irritability, responses to handling and consolability	Preterm Full-term	Construct validity: Yes	Prolonged pain Used in infants requiring sedation for mechanical ventilation
EDIN: Echelle Douleur Inconfort Nouveau-Ne Neonatal Pain and Discomfort Scale; Debillon et al (2001)[137]	5 items: Facial activity, body movement, quality of sleep, quality of contact with nurses, consolability	Preterm 25-36 wks GA	Inter-RR: 0.59-0.74 Internal consistency: 0.86-0.94 Construct validity: Yes	Prolonged pain
COMFORTneo: modified from the COMFORT behavior scale; Van Dijk et al (2009)[150]	7 items: Alertness, calmness/agitation, respiratory response (in mechanically ventilated children), crying (in spontaneously breathing children), body movement, facial tension, (body) muscle tone.	Preterm Full-term 24-42 wks GA	Inter-RR: 0.79 Internal consistency: 0.84 -0.88 Concurrent validity: Yes	Prolonged pain Sedation level

Abbreviations: CV, convergent validity; FLACC, Face, Legs, Activity, Cry, Consolability Scale; GA, gestational age; Inter-RR, interrater reliability; Intra-RR, intrarater reliability; NIPS, Neonatal Infant Pain Scale.

TABLE 2. Multidimensional Infant Pain Measures

Instruments	Items	Age Group	Reliability and Validity	Clinical Utility
Designed for measurement of acute/procedural pain				
NIPS: Neonatal Infant Pain Scale; Lawrence et al (1993)[89]	6 items: *5 behavioral*: facial expression, cry, arms, legs, and state of arousal *1 physiological*: breathing pattern	Preterm Full-term 26-47 wks GA	Inter-RR: 0.92-0.97 Internal consistency: 0.87-0.95 Concurrent validity: 0.53-0.84	Procedural pain Postoperative pain
NPAT: Neonatal Pain Assessment Tool; Fredrichs et al (1995)[151]	7 items: *3 behavioral*: state, cry, activity *4 physiological*: heart rate, blood pressure, respiratory rate, oxygen saturation	Preterm Full-term 25 wks GA-12 mos	Content validity	Procedural pain Postoperative pain
PIPP: Premature Infant Pain Profile; Stevens et al (1996)[152]	7 items: *3 behavioral:* brow bulge, eye squeeze, nasolabial furrow *2 physiological:* heart rate, oxygen saturation, *2 contextual*: gestational age, behavioral state	Preterm Full-term 28-42 wks GA	Inter-RR: 0.93-0.96 Intra-RR: 0.94-0.98 Content and construct validity: Yes The most commonly used tools in research studies	Procedural pain post-operative pain
DSVNI: Distress Scales for Ventilated Newborn Infants; Sparshot (1996)[153]	7 items: *3 behavioral:* facial expression, body movement, color *4 physiological:* heart rate, blood pressure, oxygenation, core to peripheral temperature differential	Preterm 26-35 wks GA	Content validity: Yes	Procedural pain, ie, ventilation Used in ventilated and critically ill infants
SUN: Scale for Use in Newborns; Blauer et al (1998)[154]	7 items: *4 behavioral*: central nervous system state, movement, tone, face *3 physiological*: breathing, heart rate, mean blood pressure	Preterm Full-term	Content and discriminant validity: Yes	Procedural pain, ie, intubation, catheter insertion, suctioning
PAIN: Pain Assessment in Neonates; Hudson-Barr et al (2002)[155]	7 items: *5 behavioral*: facial expression, cry, breathing pattern, extremity movement, state of arousal *2 physiological*: oxygen required, vital signs (combines aspects from both the NIPS and the CRIES into 1 scale)	Preterm Full-term 26-47 wks GA	Inter-RR: 0.73 Construct and criterion validity: Yes	Procedural pain

(continues)

TABLE 2. Multidimensional Infant Pain Measures (*Continued*)

Instruments	Items	Age Group	Reliability and Validity	Clinical Utility
BPSN: Bernese Pain Scale for Neonates; Cignacco et al (2004)[156]	9 items: *7 behavioral*: grimacing, body movements, crying, skin color, sleeping patterns, respiration, consolation *2 physiological*: heart rate, oxygen saturation	Preterm Full-term	Inter-RR: 0.86–0.97 Intra-RR: 0.98–0.99. Concurrent and CV: 0.86-0.91	Procedural pain, ie, ventilation.
FANS: Faceless Acute Neonatal Pain Scale; Milesi et al (2010)[157]	4 items: *3 behavioral*: acute discomfort, limb movements, vocal expression *1 physiological*: heart rate variation	Preterm 30-35 wks GA	Internal consistency: 0.72 Inter-RR: 0.92 Correlation with DAN: 0.88	Procedural pain Used in nonintubated infants when face is not visible
COVERS Neonatal Pain Scale; Hand et al (2010)[158]	6 items: *4 behavioral*: facial expression, resting state, body movements, crying *2 physiological*: oxygen requirement, vital signs	Preterm Full-term 27-40 wks GA	Concurrent and construct validity: Yes	Procedural pain
PASPI: Pain Assessment Scale for Preterm Infants; Liaw et al (2012)[159]	6 items: *4 behavioral*: sleep state, facial expression, limb and body movement, hand behavior (splay and fisting) *2 physiological*: heart rate, oxygen saturation	Preterm 27-36 wks GA	Internal consistency: 0.84 Inter-RR: 0.88-0.93 Correlation with VAS: 0.72-0.81 Correlation with PIPP: 0.74-0.83	Procedural pain Taiwan-version (in Chinese)
Designed for measurement of postoperative pain				
COMFORT Scale (not primarily developed for neonates); Ambuel et al (1992)[160]	8 items: *6 behavioral*: muscle tone, facial tension, alertness, calmness/agitation, respiratory behavior, physical movement *2 physiological*: mean arterial blood pressure, heart rate	Preterm Full-term 0-3 years old	Inter-RR: Yes Content validity: Yes	Postoperative pain Distress associated with pain, ie, in ventilated infants
PAT: Pain Assessment Tool; Hodgkinson et al (1994)[161,162]	10 items: *5 behavioral*: posture/tone, sleep pattern, expression, color, cry *4 physiological*: respirations, heart rate, oxygen saturation, blood pressure *1 nurse's perception* of infant's pain Score: ≤4 no pain 20 = worst pain	Preterm Full-term 27-40 wks GA	Inter-RR: 0.85 Face, construct validity: Yes Correlation with CRIES: 0.76	Postoperative pain

(continues)

TABLE 2. Multidimensional Infant Pain Measures (*Continued*)

Instruments	Items	Age Group	Reliability and Validity	Clinical Utility
CRIES: Krechel et al (1995)[163]	5 items: Crying, requires O_2 for saturation, increased vital signs (HR and BP), expression, sleepless	Preterm Full-term to 15 months	Inter-RR: r=0.72 Construct and discriminant validity: Yes	Postoperative pain
MIPS: L Modified Infant Pain Scale; Buchholz et al (1998)[164]	13 items: *10 behavioral*: sleep, facial expression, cry, motor activity, excitability and responsiveness to stimulation, flexion of fingers and toes, suckling, overall tone, consolability, sociability *3 physiological*: heart rate, blood pressure, oxygen saturation	Full-term	Inter-RR: 0.85 Criterion validity: Yes	Postoperative pain
MAPS: Multidimensional Assessment Pain Scale; Ramelet et al (2007)[165]	5 items: *3 behavioral*: facial expression, body movements, state of arousal *2 physiological*: vital signs, breathing pattern	Neonates infants to 31 mos	Internal consistency 0.68 Inter-RR: 0.68–0.91 Content, concurrent, convergent validity: Yes	Postoperative pain
Designed for measurement of prolonged/ongoing pain				
N-PASS: Neonatal Pain, Agitation, and Sedation Scale; Hummel et al (2008)[138]	5 items: *4 behavioral*: Crying/irritability, behavior/state, facial expression, extremities/tone, *1 physiological*: vital signs (HR, RR, BP, Sa_{O_2})	Preterm Full-term 23-40 wks GA	Internal consistency: 0.85–0.95 Inter-RR: 0.88-0.93 Test-retest reliability: 0.87 Correlation with PIPP: 0.61-0.83	Ongoing pain, ie, ventilation Sedation level Postoperative pain Procedural pain

Abbreviations: BP, blood pressure; CRIES, Crying, Requires Oxygen, Increased Vital Signs, Expression, Sleep Scale; CV, convergent validity; DAN, Douleur Aiguë du Nouveau-né; GA, gestational age; HR, heart rate; Inter-RR, interrater reliability; Intra-RR, intrarater reliability; RR, respiration rate; VAS, Visual Analogue Scale.

analysis in audible and inaudible crying of infant pain may provide us with more understanding of this phenomenon.

Observations of gross motor responses including body movements of arms, legs and trunks, and whole body, finger splay and fisting,[34] and attempts to withdraw from a painful stimulus have also been used to assess pain levels during different phases of a heel lance procedure.[35] However, very low-birth-weight or sick infants may become flaccid in response to a painful stimulus because they may not have the energy resources to respond as more mature infants do.[36] This does not mean they do not feel pain and a careful observer will note when the flaccidity occurs as a sign of the infant's tolerance to the painful event. Although increased motor activity is a characteristic of pain and responses of body movements have been composited in some pain tool,[34,37] they are not commonly used as pain indicators due to the lack of available objective measurements and less specificity of activity and movement to pain. The flexion withdrawal reflex is a clear, distinct withdrawal of the limb that can be evoked by a noxious stimulus to the heel and it has been found to correlate with the severity of a stimulus and the latency, amplitude, and duration of the cutaneous withdrawal reflex in preterm and full-term neonates.[38] In addition, young infants have lower thresholds, more exaggerated, and longer-lasting reflex muscle contractions in responses to pain.[39] Studies have used flexion reflex responses as pain measures in procedural pain and postoperative pain in neonates.[40]

Observation of behavioral states, such as sleep-wake alterations, have been identified in infants following painful procedures such as a circumcision without anesthesia.[41] Moreover, painful procedures are often followed by prolonged periods of non–rapid-eye-movement sleep,[42] increased wakefulness[43] and agitation,[44] and immature sleep-wake cycling.[45,46] These findings suggest that painful procedures may have prolonged effects on the neurologic and psychosocial development of infants. Behavioral states are also assessed and included in many pain tools as contextual factors of pain. Several reports showed that the infant in a sleep state will have less behavioral (ie, facial actions) and physiological pain responses than an infant in an awake state,[31,47,48] and cortical responses to pain stimuli were significantly greater in awake infants than in sleeping infants.[49] These findings suggest that infant behavioral state is an important factor in pain response and in pain assessment. Although behavioral responses provide us with outward signs of pain, physiologic responses provide us with the body's more generalized response.

Physiologic and Autonomic Responses

Physiological responses to painful stimuli include increases in heart rate, respiratory rate, blood pressure, intracranial pressure, and palmar sweating, and are accompanied by decreases in transcutaneous oxygen saturation, vagal tone, and peripheral blood flow.[13,22,40,50--54] Autonomic responses include changes in skin color, nausea, vomiting, gagging, hiccoughing, diaphoresis, palmar sweating, and dilated pupils.[55] During episodes of vigorous crying, oxygenation may increase, but oxygen delivery to cerebral tissues may be compromised even though the oxygen content of the blood remains stable.[56] Physiological indicators cannot be used alone to determine pain levels because of the lack of sensitivity and specificity to pain, but these responses are commonly observed simultaneously with behavioral and other pain indicators further supporting the use of a multidimensional approach to pain assessment and management. Beyond behavioral and physiologic responses to pain, one must also consider biochemical responses.

Biochemical Responses

Hormonal and metabolic changes can be observed during and following a painful procedure, including increased secretion of catecholamines (ie, norepinephrine) and epinephrine, glucagon, and corticosteroids or cortisol,[54,57] and decreased prolactin, insulin, and immune responses.[21,58] The disturbed catabolic states induced by pain may be more damaging to younger and more immature infants who have higher metabolic rates and less nutritional reserves than older children and adults. Neonatal stress responses have been found to be 3 to 5 times greater than those in adults, although the duration was noted to be shorter, possibly because of the lack of deep anesthesia.[57] Stress hormones in serum and saliva have been measured as indicators of pain perioperatively, and during heel stick and mechanical ventilation.[54,59-61] Nevertheless, biochemical measures may be difficult to use routinely in the critical care setting because of the lack of feasible laboratory analysis. Investigations of novel, reliable, and clinically feasible biomarkers are needed to provide objective data in pain assessment and to evaluate the effectiveness of the treatment regimen for relieving infant pain.

Infant Contextual Parameters in Pain Assessment

One of the major challenges in pain assessment is that contextual factors may alter infants' biobehavioral responses to pain. Recently, in a systematic review, Sellam et al[7] examined this topic. Although the results still remain inconclusive, many studies have shown that contextual factors such as infant age, previous pain experiences, gender, and health status play an important role in pain responses, especially in preterm infants, and must be considered in the measurement of pain.[31,47,50,62--65] Each is discussed in more detail in the following sections.

Gestational and Postnatal Age

Behavioral responses to pain were found to be significantly correlated with infants' gestational age[22,35,65-68] and postnatal age[31,50,63] with dampened responses in younger less-mature preterm infants versus those who are more mature infants. However, objective observation of physiological responses is less clear in preterm infants. Some studies reported a significant effect of gestational age on heart rate[35,66] and oxygen saturation,[22,66] but many studies do not find an age-related impact for physiological responses to pain.[64,67-70] Several pain instruments included both behavioral and physiological indictors, such as the Preterm Infant Pain Profile (PIPP), and findings from these studies indicate that younger gestational age infants were less likely to demonstrate easily observable pain responses.[31,71,72] The developmental factors of the nervous-muscular systems can explain these varied pain responses among different infant age groups. Young preterm infants have less muscular strength, posture, tone, and body movement than more mature infants and, therefore, are more likely to demonstrate fewer facial actions related to pain stimuli.[22,72]

Previous Pain Exposure

Studies report that previous pain exposure is significantly associated with altered behavioral responses and autonomic pain reactivity. Infants experiencing higher numbers of invasive procedures since birth might have reduced facial actions to pain[64,66,70] and have lower PIPP scores.[31,71] The relationship between the number of prior painful procedures and physiological indicators is not consistent. One study found that the pain experience was significantly related to heart rate variability (HRV),[66] whereas another reported a moderate but nonsignificant correlation with heart rate.[64] Other studies have not found a correlation of pain experience with heart rate, oxygen saturation, and/or the PIPP scores.[31,50,70,73] Early pain exposure in very younger preterm infants may alter the autonomic substrate, resulting in infants who are in a perpetual state of stress and thus making acute pain assessment more difficult. A recent study showed that higher numbers of skin breaks were significantly associated with reduced white matter and subcortical gray matter maturation in preterm infants.[74] These findings may demonstrate that early and repeated pain stimuli overactivate the immature neurons, which are susceptible to excitotoxic damage,[74] and may also explain how the previous pain exposures alter the infants' behavioral responses.

Gender

Few studies reported gender difference in pain responses in neonates. Guinsburg et al[75] found that female neonates of both preterm and full-term expressed more facial actions than male infants during capillary punctures. The finding may be related to differences in pain processing and/or pain expression among genders. More research is essential to understanding these differences.

Health Status

A number of studies investigated the association of health status, including infant severity of illness and neurologic impairment, with pain responses in preterm infants. The results are not consistent. Some studies found that severity of illness affected the cry responses to pain[47] and had small but significant negative association with PIPP scores.[71] However, many studies found no associations between severity of illness and pain responses[50,64,66,70,76] and between neurological impairment and pain responses[63,65]; only 1 study that found neurologically impaired infants had more tongue protrusion at heel lance.[77] Based on the current available research, health status does not seem to readily affect the infants' biological substrates for pain, and further studies are needed in this area to understand the relationship between health status and pain expression.[7]

Characteristics of the Painful Stimuli

The characteristics of pain stimuli, such as the source or cause of the pain, location, and timing of pain, influence perception of and response to pain. Neonatal infants can have differential responses to procedural pain (eg, heel stick, venipuncture, and suction), to ongoing pain (eg, mechanical ventilation), or to operation/postoperative pain (eg, circumcision and other surgeries). Infants show increased magnitude of behavioral and physiologic responses to increasingly invasive procedures, and even very prematurely born infants respond to pain and differentiate stimulus intensity.[44] The duration, origin, and location of the painful stimulus and the context within which the painful stimulation occurs, such as the environment[78] and sound,[79] can also influence infant pain responses. Most research with preterm infants has focused on the responses to acute pain caused by a single noxious stimulus, but pain commonly occurs over a prolonged period or is recurrent and, as such, makes pain assessment more difficult to differentiate. Because of the tremendous plasticity within pain-processing systems, contextual factors significantly affect infants' experiences of pain; therefore, these factors need to be assessed and considered in tandem with pain responses.

Characteristics of the Clinical Observers

Neonates cannot speak and advocate for themselves when they experience pain. Likewise, care providers face enormous challenges because self-report is considered the gold standard for pain measurement in other populations. Health providers' knowledge, ability, and attitudes toward neonatal pain are significant factors in observation, and using appropriate pain tools to recognize a neonate's pain.

Importantly, how these caregiver characteristics impact decision making is a major factor in effective pain relief. A number of pain surveys from around the world showed that many nurses and physicians assessed premature infant pain without using pain tools regularly,[80-82] and while pain assessment is often considered the fifth vital sign, only some NICUs have practice standards in place that routinely assess pain during mechanical ventilation and after surgery.[83,84] Findings show that some nurses were concerned about the accuracy of the pain tools, and they tend to rely on their own instincts to assess infant pain.[85] Inadequate staff training regarding pain assessment and lack of evidence-based pain management guidelines have been identified as barriers to using pain tools.[81,82,85] Nurse-physician collaboration, nurses' work assignments, and autonomy in decision making may also predict evidence-based pain care.[86]

PAIN ASSESSMENT TOOLS AND NEW MEASUREMENT TECHNIQUES

Unidimensional and Multidimensional Tools

Since the 1980s, more than 40 infant pain measurement scales have been developed. The unidimensional tools (Table 1) such as the Neonatal Facial Coding System[48] and the Behavioral Pain Score[87] are composed of a single pain indicator (ie, facial activity) or a unitary dimension of pain (ie, behavioral indicators). The multidimensional tools (Table 2) such as the PIPP[88] and the Neonatal Infant Pain Scale (NIPS)[89] measure pain with a composite score that includes a variety of physiologic, behavioral, and contextual indicators. Characteristics of the quality of measurement instruments/tools are known as the psychometric properties and include reliability, validity, sensitivity, and specificity. An accurate measurement of pain intensity is based on the properties that enhance its use in a specific population and particular research design or clinic setting. The characteristics for each pain scale are summarized in Tables 1 and 2. Pain measurement in preterm infants remains an enormous challenge for practitioners because no gold standard instrument for pain assessment during early infancy exists,[90,91] and exceptional attention needs to be given to confounding factors including age, behavioral state, and previous painful experience. Multidimensional pain measurements have been viewed to be more accurate than single parameters because of the complex nature of pain; however, the instruments are often lengthy and sometimes difficult to administer in the clinical setting. Some current research reported that unidimensional scales including the Neonatal Facial Coding System are more sensitive for the identification of pain in healthy term infants than the PIPP, a multidimensional tool.[92] Although there are many newly published pain tools for use in both preterm and term infants, many of them largely overlap with existing tools.[93] Novel instruments, especially those targeting pain biomarkers and measures of cortical responses to pain, may need to be further developed.[93,94] Studies are also needed to examine the clinical feasibility of pain tools during different pain conditions, that is, ongoing pain, and within varying neonatal populations.[95]

New Techniques for Pain Measurement

Over the past several years, research has continued to explore more objective approaches to pain assessment, such as HRV and skin conductance (SC) measurement. In addition, brain-oriented techniques including near-infrared spectroscopy (NIRS), electroencephalography (EEG), and magnetic resonance imaging (MRI) have been used recently to measure neonatal pain responses at the cortical level. These technologies have the potential to improve accuracy of infant pain assessment and measurement and provide clinicians and researchers with more discrete direction in pain intervention and more accurate continued decision making. The existing evidence to support the integration of HRV, skin conduction, and brain-oriented approaches is each described later.

Heart Rate Variability

Heart rate variability is defined as the cyclic changes or fluctuations in the R-to-R intervals that occur with respiration.[96] The R-R interval can be analyzed to provide a sensitive, noninvasive measure of autonomic input to the sino-atrial node of the heart. Heart rate variability is an index of the balance of sympathetic and parasympathetic control on heart rate[97] and has been used as a sensitive index of stress caused by pain reactivity.[98] Two approaches have been used to measure and analyze HRV data: the time domain and the frequency domain analysis. Time domain analysis is a general measure of autonomic nervous system balance that is based on the measurement of the standard deviation of heart period, and the frequency domain analysis delineates parasympathetic from sympathetic components of autonomic control with power spectral analysis.[96] Spectral analysis of the transformed ECG data generates 3 components of clinical interest[96,99]: the low-frequency (LF, 0.04-0.15 Hz) component, an index of primarily sympathetic activity with some parasympathetic input; the high-frequency (HF, 0.15-1.0 Hz) component, an index of parasympathetic activity; and the LF/HF ratio, an index of autonomic balance.[97,100] Lower values for the LF/HF ratio indicate a better balance between the 2 systems.[99,101,102] Studies examining the effects of kangaroo care on reducing pain demonstrated that infants in the intervention condition had better balanced autonomic activity than in the control condition

during a heel stick procedure.[101,103] Heart rate variability is an appropriate measure of response to acute pain and prolonged pain in neonates[22,104-106]; however, given a lack of the availability of monitoring devices, it may not be clinically applicable.

Skin Conductance

The measurement of SC is based on stress-induced sweating of the hand palms and/or foot soles. Skin conductance activity is a measure of the psychogalvanic reflex response indicating that the sympathetic nervous system is activated and sweat is released on the skin surface in response to stress when pain occurs.[107] With the sympathetic excitation and filling and reabsorption of sweat in the sweat glands, the electrodermal activity of the skin increases and a measurable wave of increased SC can be detected. The SC device can monitor the activity continuously and calculate the mean peaks per second over an interval of 10 to 60 seconds.[93] Skin conductance has been shown to be a promising, noninvasive physiological marker of pain and stress in term infants,[106,108-111] but conflicting results were reported from studies that included preterm infants.[112,113] Some studies reported that SC lacks specificity for discriminating between the painful and nonpainful procedures,[108,112] and SC increased when the infant was given glucose as an analgesic before heel lancing.[113] Skin conductance was also found to be correlated with infant body temperature[109] and is sensitive for body movement artifacts.[114] The wide range of sensitivity and specificity for SC has not made it readily acceptable for clinical practice,[93] especially in preterm infant, and as such it needs further investigation.

Brain-Oriented Approach

The principal processor of internal and external sensory experiences including pain is in the brain. Advances in technologies for measuring central pain responses provide a window into the infant brain and for evaluating changes in cortical pain processing related to behavioral and physiologic pain responses.[94] Several recent studies have reported using NIRS,[49,115-119] scalp EEG,[115,120-122] and MRI[74] neuroimaging techniques to measure somatosensory and frontal cortex activation.

The optical technique of NIRS is based on the principle of infrared light passing through human tissue, by which it can detect subtle changes in the concentration of the oxygenated and deoxygenated hemoglobin in the brain to monitor hemodynamic and oxygenation adjustments related to the cerebral cortical processing of specific stimuli.[94] Recent studies in preterm and full-term infants reported that painful stimuli cause hemodynamic changes in specific cortical regions, that is, the contralateral somatosensory cortex.[49,117,119,123] Preterm infants born as early as 25 weeks' gestation were found to have increased oxygenated hemoglobin in the somatosensory cortex in response to heel stick.[49] The cerebral hemodynamic responses depended on the gestational age and awake/sleep states of the infants, with less robust responses in younger neonates than older ones, or neonates asleep than awake.[49] NIRS has been also found to be moderately correlated with PIPP scores and facial expressions in 25- to 43-week postmenstrual aged infants,[123] but not associated with the physiologic responses and the Face Leg Activity Cry Consolability pain scores in critically ill infants younger than 12 months.[117] Additional studies are needed to determine the feasibility, specificity, and sensitivity of NIRS as a novel physiological assessment instrument in different painful conditions.

Scalp EEG has been used to assess cortical responses to pain stimuli in both full-term and preterm infants. One study measured EEG during a noninvasive, but noxious stimulus in neonates given sucrose or water, and found that relative right frontal EEG activation was demonstrated only in the water group, compared with "negative" cortical activation in the sucrose group.[124] A time-locking technique of EEG was recently used by a group of researchers demonstrating an evoked cortical response after a single painful stimulus in preterm and full-term infants.[120,121,125] Fabrizi et al[122] systematically mapped the maturation of tactile and nociceptive responses in the developing brain from 28 weeks' gestation preterm infants to normal full-term infants. Findings indicated that preterm infants less than 35 weeks' gestation had a dominant response of nonspecific neuronal bursts to both touch and noxious stimuli, and infants after 35 to 37 weeks' gestational age had specific somatosensory potentials for the 2 modalities of stimulation.[122] In another study, a multimodel measurement system was tested with synchronous recording of muscle and central nervous system activity with surface electromyography, EEG, and NIRS, and with behavioral and autonomic responses during noxious heel lance and touch stimuli.[115] The system showed a high sensitivity and specificity for both types of stimulation and provided reliable and reproducible measurements on more than 100 test occasions.[115] More research is needed to explore the field of pain assessment with EEG for clinical and research purposes.

One prospective longitudinal study applied noninvasive MRI for investigation of procedural pain-related stress in association with abnormal brain maturation.[74] The results demonstrated that higher numbers of skin breaks were significantly associated with reduced white matter and subcortical gray matter maturation, and early but not later pain exposure was a significant predictor of reduced white matter in preterm infants during their NICU stay. Another retrospective study also reported that tissue-damaging

procedures were associated with altered brain metabolites on MRI in full-term infants.[126] Magnetic resonance imaging technique needs further investigation to provide objective assessment of pain-related brain alteration and further guide effective interventions for managing procedural pain in the NICU.

CHALLENGES IN NEONATAL PAIN ASSESSMENT AND MEASUREMENT

Behavioral and Biophysiological Responses to Pain

The dissociation between physiologic and behavioral responses is a perplexing challenge in neonatal pain assessment. Although most infants show both behavioral and physiological responses to pain, these 2 groups of measures are either uncorrelated or weakly correlated across many situations and studies.[127-130] Physiologic measures alone may not be specific to pain and they may or may not increase along with behavioral responses. Behavioral responses generally are not only more consistent and specific to pain but also present in some nonpainful situations. Behavioral responses may diminish, but physiological responses may remain elevated or even increase in some situations. The inconsistency of pain responses across painful situations is difficult to explain. This dissociation impedes the decision making about the effectiveness of interventions as clinicians are uncertain whether to rely most heavily on behavioral, physiologic, or a composite of pain outcomes. Thus, it has been suggested that physiological indicators may need to be kept distinct from behavioral indicators when measuring pain outcomes.[127]

Some high-risk infants do not show any response to tissue-damaging events when not given analgesics or other interventions.[31] This phenomenon is especially perplexing because it is not known whether the infant is not experiencing pain or whether the infant actually feels the pain and simply cannot muster a response. Although facial actions have been considered as one of the most important pain indicators, infants with neurological impairments may have reduced facial activity, and care providers may rate physiological responses as more important pain indicators.[15] Very young preterm infants may also not display a change in facial expression but have evoked cortical pain responses.[123] Lack of pain response is puzzling for clinicians and researchers. They may not make decisions about the effects of pain interventions and may be withholding analgesics and other interventions on the basis of nonresponse when the infant is truly in pain. Therefore, when using any pain measure, the contextual factors including the infant's development stage, health condition, and the painful situations must be considered.

Acute Versus Prolonged/Cumulative Pain Assessment

The majority of the current pain tools were developed from studies of neonates who experienced acute painful procedures. Methods of measuring persistent, prolonged, or cumulative pain have been largely uninvestigated or at best underinvestigated. When neonatal rats experienced persistent peripheral inflammation, which is similar to repetitive heel sticks in human infants, their spinal neuronal circuits exhibit increased input, segmental changes in nociceptive primary afferent axons, and altered responses to sensory stimulation as adults.[131,132] Repetitive or prolonged exposure to pain and stress is believed to similarly permanently alter the human infant's neuronal and synaptic organization.[4,133-135] In comparison to acute pain, signs of prolonged or ongoing pain tend to be more subtle, leading to underrecognition and undertreatment of pain.[95] Preterm infants, especially young preterms, may not display the signs of acute pain when they experience persistent invasive procedure, because they have limited energy reserves and cannot maintain the psychophysiological activation triggered by pain stimuli.[136] Two assessment tools have been developed for prolonged pain in neonates, the EDIN (Échelle Douleur Inconfort Nouveau-Né)[137] and the N-PASS (Neonatal Pain, Agitation, and Sedation Scale)[138,139] (Table 2). Additional psychometric testing in large trials with different neonatal populations is still need for both tools. Accurate, reliable, and valid pain assessments are essential to guiding the management of acute and prolonged pain in early life.

Bedside and Research Feasibility of Assessment Tools

Bedside infant pain assessment has become commonplace because of its significance and regulatory demands, but the integration of assessment and measurement into routine practice remains problematic. The majority of the current pain measurement tools were originally developed for research purposes and, as such, have not been readily available at the bedside.[93-95] More research is needed to establish sufficient clinical utility, sensitivity, and specificity for pain scales to be recommended for inclusion in routine practice. As discussed previously, when assessing infant pain, healthcare providers must take into account infant contextual indicators (eg, age, health status, and behavioral status), pain characteristics (eg, acute, persistent, and postoperative), and interpretation of the association of behavioral and physiologic responses in their assessment. In comparison to monitoring other vital signs, no single pain instrument is available for bedside use that includes a composite of all the aspects of pain indicators. The complexity of pain measurement often challenges the caregiving team and requires more

education and training to best integrate pain tools into routine practice. Based on our recent national survey,[140] neonatal nurses' perceptions of barriers to effective pain assessment included inadequate knowledge, not enough time, and lack of trust in the pain assessment tools. Therefore, we must continue to look for ways to best ensure knowledge transfer about pain assessment and management from research to practice.[95]

CONCLUSIONS

The goals of pain assessment and measurement in neonates are to describe the phenomenon of pain, diagnose and predict the need for intervention, and evaluate the effectiveness of pain interventions. Currently existing controversies about infant pain assessments include dissociated biobehavioral response systems, lack of observable indicators because of depleted energy sources, and a shift from acute to ongoing or chronic pain. Although more than 40 pain tools for use in both preterm and full-term infants have been published, many of them were devised solely for the research purposes, and many of the newly developed tools largely overlap with existing tools. Still, the integration of pain assessment and measurement into daily practice remains problematic. Novel instruments, especially those targeting pain biomarkers and measures of cortical responses to pain that can objectively measure pain and be trusted by care providers, need to be further developed and studied. Bedside noninvasive techniques such as HRV, SC, NIRS, EEG, or other technologies are showing promising results in their usefulness to detect autonomic and cortical activation related to painful events, but studies are necessary to examine their clinical feasibility. Studies are also necessary to examine the clinical feasibility of pain tools during different pain conditions (ie, ongoing pain), and within varying neonatal populations. There is no universally accepted gold standard to measure infant pain. Determining the presence of pain in the neonatal population remains problematic for healthcare professionals because of the subjective nature of pain, the lack of accurate indicators of pain, and the infants' inability to communicate their pain. The accurate measurement of neonatal pain is nevertheless imperative for ensuring comfort during the diagnostic process and in evaluating the effectiveness of pain treatments. The "golden rule" of pain assessment must be as follows: what is painful to an adult is painful to an infant unless proven otherwise. As described in our conceptual framework (Figure), the basic tenet of appropriate pain measurement is choosing "the right tool for the right patient," meaning that the pain measurement instrument used must be based on the developmental age and on the type of pain or medical condition for which the specific pain-measurement tool exists (ie, procedural versus postoperative pain). Investigators and clinicians need to select the most appropriate measures for their particular purpose and reestablish or further establish the psychometric properties in different neonatal population and varying health status and clinical situations. Assessment is the cornerstone of adequate pain management; it is the responsibility of health researchers and practitioners to develop, test, and use the best measures to assess infant pain. It is our premise that best neonatal outcomes occur when pain is well managed and every effort must be made by caregivers to relieve and abate infant pain.

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