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Assessment of pain in newborn infants

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ABSTRACT

Hospitalized newborn infants experience pain that can have negative short- and long-term consequences and thus should be prevented and treated. National and international guidelines state that adequate pain management requires valid pain assessment. Nociceptive signals cause a cascade of physical and behavioral reactions that alone or in combination can be observed and used to assess the presence and intensity of pain.

Units that are caring for newborn infants must adopt sufficient pain assessment tools to cover the gestational ages and pain types that occurs in their setting. Pain assessment should be performed on a regular basis and any detection of pain should be acted on. Future research should focus on developing and validating pain assessment tools for specific situations.

1. Introduction

There is no longer any doubt that newborn infants experience pain, and that this pain can have negative consequences on short and long term outcomes. Ever since the publication of the first national and international guidelines for neonatal pain management [1,2], pain assessment has been promoted as an essential part of adequate pain management. The purpose of pain assessment is to judge if an infant is in pain and if so, take action to reduce or remove that pain. Pain assessment is also needed to evaluate the effect of interventions aimed at pain relief, both on individual and institutional levels.

2. Types and sources of pain

The International Association of Pain (IASP)'s classical definition of pain from 1969, as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” [3], has since been discussed in relation to how newborn infants can communicate their experienced pain and how it can be interpreted by caregivers [4]. Traditionally three types of neonatal pain have been mentioned when discussing how to assess pain: acute/procedural pain, acute/prolonged pain (including post-operative pain), and chronic pain. Having only these three definitions of pain-types has limited the development of a more finely-tuned pain assessment, and thus in 2017 Anand proposed an updated uniform taxonomy, based on temporal features, character of pain and secondary effects [5]. Built on these three features he suggested the following terms to classify neonatal pain: Acute episodic, Acute recurrent, Prolonged, Persistent, and Chronic.

All infants, even those considered to be healthy, undergo painful procedures immediately after birth and throughout infancy as part of routine preventive practices. Exposure to pain and repeated painful procedures is even greater in sick and/or preterm newborn infants due to their medical condition but mostly as a result of the care and treatment they receive. Numerous studies show that hospitalized neonates undergo 10–15 painful procedures daily, both in industrialized [6,7] and in developing [8] countries, and often without any associated pain relief [9]. Besides surgery and mechanical ventilation, the most common sources of pain are skin-breaking procedures: heel lance, venipuncture and placement of venous catheters, and non-skin-breaking procedures: endo-tracheal suctioning and insertion and manipulation of CPAP-prongs [10].

3. Consequences of pain

The groundbreaking studies by Anand et al. in the late 1980's demonstrated that the provision of sufficient analgesia reduced negative short-term outcomes in neonates undergoing surgery, which previously had been performed with just muscle-relaxant [11–13]. The stress caused by pain leads to alterations in heart rate, breathing rate, blood

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pressure, intracranial pressure, and to hormonal and metabolic changes [14,15]. This in its turn can lead to impaired wound healing, lower immune response and/or cerebral lesions. In addition to the immediate stress and physiological instability associated with pain, more recent studies have shown that greater exposure to repeated painful procedures in early life is associated with long lasting adverse effects such as alteration of later pain response, delayed postnatal growth, poor early neurodevelopment, and altered brain development [16–18].

4. Pain signaling

In adult and cognitive intact persons self-report is the gold standard for detecting the presence, type and intensity of pain, but in non-verbal persons like newborn infants, responses in different bodily systems must be the base for pain assessment. When peripheral pain receptors (nociceptors) are affected by mechanical (or chemical or thermal) stimuli - usually tissue damage from e.g. a heel lance - pain signals are transferred in nociceptive pathways, to the spinal cord. There, a spinal reflex response is induced with the purpose to withdraw the affected limb, away from the threat/hurt. Simultaneously pain-signals are sent to different areas in the brain where further physiological, hormonal and behavioral responses are produced [19]. The purpose of these reactions is to protect the human being from further damage, but immaturity, illness, brain deprivation or sedation affects the ability to react adequately [20]. This means that pain assessment methods that are built on these reactions also must take contextual factors like gestational age and medical status into account. This paper focus on pain assessment in newborn infants, i.e. up to 4–6 weeks after full term birth. Some signals and pain assessment tools are valid also for older ages but most research has been in the preterm population.

The normal response to a painful stimulus is a vivid activation of mechanisms to facilitate the avoidance of hurt and danger. Repeated pain signaling will however change these reactions with an increased sensitivity – hyperalgesia – and even response to non-painful stimuli – allodynia [21,22]. If the pain continues and become prolonged or even persistent the reactions might be blunted [23]; as such absence of - or lower - pain signals cannot be assumed to equate to the absence of pain. Given this possibility, different pain assessment methods that are developed and validated for specific situations should be considered when evaluating acute or prolonged pain [24].

4.1. Biomarkers

Table 1 demonstrates physiological and neurophysiological reactions, also called biomarkers [25,26], that can be used as indicators of pain in infants. Given that many of these signs are dependent on the infant's ability to react, and thus both an increase and decrease can be seen. Normally a healthy robust infant born at term age will react with an activation of the fight-flight system including increased heart and respiration rate, dampness of palmar and plantar skin etc., whereas infants delivered preterm or ill, or those in a sleep-state will exhibit a lower or reverse response [15,27,28]. While the activation of the fightand flight mechanism includes the release of stress hormones, e.g. catecholamines and corticosteroids [25], the requirement of laboratory analyses makes them less appropriate for clinical practice and they will not be further presented in this paper. Pain signals can also be detected with modern neuro-imaging techniques like electroencephalography.

EEG, near-infrared spectroscopy (NIRS), or functional magnet resonance imaging (fMRI) [29]. Despite these methods holding promise for improved pain assessment in non-verbal infants, considerable challenges remain regarding the pain specificity, clinical utility and feasibility of these techniques [30,31]. Detailed discussion of these techniques is beyond the scope of this paper.

4.2. Behavioral pain signaling

Pain leads to a number of responses in the infant's behavior, that can be observed and contribute to assessment of presence and intensity of pain [15]. These responses include changes in body movements and tone, grimacing, crying or vocalization, changes in sleep-wake state and affected attention/communication. Similar to physiological responses, prematurity, illness or lower wake-state can lead to more diffuse behavioral signs when compared to those exhibited by healthy full-term infants. It is suggested that behavioral signs, especially facial expressions, are more pain specific than physiological signs, which can alter in response to many situations: pain, stress, discomfort or touch [46] (see Table 2).

4.3. Pain assessment tools

Infant pain measures are often classified as being either unidimensional or multidimensional. Unidimensional measures include a) single item, e.g. changes in heart rate, b) single domain when more than one item in the same domain is included, e.g. facial expressions, or c) multiple domain with items from different domains within the same dimension, e.g. movements and facial expressions which are both in the behavioral dimension. In contrast, multidimensional measures, often referred to as composite, include items from more than one dimension, often behavioral, physiological reactions and infant factors e.g. state. Some studies suggest that behavioral items have greater effect size, i.e. influences the overall pain assessment more that their physiological companions when combined in the same instrument [54,55].

There have been several attempts to develop reliable, valid and clinically feasible instruments for newborn infants. To date, around 40 instruments have been published [56], with varying degrees of psychometric evaluation [57]. In Tables 3–5 we list instruments most commonly reported as part of research studies, considered to be reliable and valid in this population, and those with the greatest uptake across clinical settings worldwide. We have excluded instruments that have been locally developed and adapted, or those considered to be “out-

Table 1
Physiological and neurophysiological reactions to pain. For a comprehensive overview, see Refs. [25,26], whereas more specific references if necessary are given in the table.

	Effect from painful stimuli	
Blood pressure	Increase or decrease	
Heart rate	Increase or decrease, bradycardia	
Cerebral oxygenation	Increase of oxy-haemoglobin (HbO2) and decrease of deoxy-haemoglobin (HHb))	[32,33]
Electroencephalography (EEG)	Evoked response over central brain regions	[34,35]
Flexion withdrawal reflex	Threshold increases in latency and amplitude	[36,37]
Heart rate variability	Decreased spectral power in the high frequency band	[38–40]
Intracranial pressure	Increase	[41]
Oxygen saturation	Decrease	
Respiration rate	Increase or decrease, apnea	
Skin color	Increase (red) or decrease (pale)	[42]
Skin conductance	Increased number of peaks/second, amplitude of peaks and area under curve	[43–45]

Table 2
Behavioral reactions to pain. For a comprehensive overview, see e.g. Ref. [15], whereas more specific references if necessary are given in the table.

	Effect from painful stimuli	
Communication	Avoidance of eye-contact, locking of gaze or drifting away	
Crying, vocalization	Longer duration, changes in quality; fussiness, "silent cry"	[47,48]
Facial expressions, grimacing	Presence and duration of e.g. brow bulge, eye squeeze, naso-labial furrow, open lips, horizontal mouth stretch, vertical mouth stretch, lip purse, taut tongue and/or chin quiver	[49,50]
Limb movements	Presence and duration of avoiding or more indistinct limb movements; hand movements like fisting or finger splaying	[15,51–53]
Muscle tone	Increased or decreased	
Sleep-wake state	Quality of sleep, hyper-alertness	

dated" and replaced with successors, or where no further validation studies are published. Some authors have also suggested that the body movements associated with NIDCAP®-observations can be used to assess pain [51,58], whereas other did not find them pain-specific enough and thus should not replace e.g. facial expressions as pain-measure [59].

4.4. Subjective pain rating

Besides giving scores to observable or measurable pain signs, some pain instruments, like COMFORTneo and PAT, includes 1–2 items where the person who is performing the assessment should give his or her own rating of pain and distress [68,77]. Bellieni et al. argued that pain *detection* is more important than pain scoring in the everyday clinical situation, and thus suggested a two-point method for this. First step is to judge if the situation could be painful and secondly to look for a reaction, e.g. crying or changes in heart-rate [82]. This can however be hard. In a study from a British NICU without routine use of validated pain tools, 50% of the staff found it difficult to determine whether a baby was in pain or not [83].

5. Pain assessment by parents

In a family centered neonatal care approach, it is natural to engage parents in pain management and pain assessment, and they have also expressed this wish [84,85]. To ensure infants optimal pain management built on parental assessment, it is important to know if the parents are able to perform an adequate pain assessment. In two studies from Brazil, mothers without previous training were able to identify signs of procedural pain [86], primarily related to crying and restlessness. Interestingly, these mothers did not consider facial expressions as being associated with pain signaling [87]. In a study comparing parents' and health care professionals' ability to recognize photographs of a "pain face" (i.e. no relation between the newborn infant and the observer), the parents were slightly more able to recognize the pictures of a painful situation [88], whereas parents in clinical studies tend to rate pain lower than health care professionals [89], or perceive a higher degree of distress than of pain in their infants [90]. Boyle et al. found that parents thought it was easy to assess their infant's *comfort*. The word pain was not used when asking the parents, which indicates the importance of a common terminology. The parents also believed that it was easy for the staff to assess their infant's pain, which was not confirmed by the staff in the same study [83].

In studies on older children the parents underestimated their child's acute or postoperative pain, which per se leads to a risk of undertreatment [91–93]. Built on an interview-study with parents, Loopstra et al. have suggested a model for parental assessment of acute child pain, built on how parents can regulate their own feelings and be open for the baby's pain cues [94].

6. Assessing pain experiences or pain responses?

While it was previously believed that infants' reactions to pain were simply reflexive, we now know that all the systems needed for ascending pain processing are present early in the fetal development (whereas the descending pain modulatory functions mature later). We still have little knowledge whether a newborn infant is able to *experience* pain in a more affective way, but recent studies using functional brain imaging indicate that the brain regions that encode sensory and affective components of pain are active in infants, suggesting that the infant pain experience closely resembles that seen in adults [95]. For the time being, methods built on pain *perception* does not seem to have a clinical utility or advantage over those measuring pain *responses* [96].

7. Requirements on pain assessment

No matter which tool we choose for pain assessment it must be valid (measure what it is intended to measure), and reliable (give the same results if repeated by another person or at another time under the same conditions) for the specific population being assessed and feasible to use in the clinical situation [97]. This includes how much time and resources it takes to acquire, implement, train the staff and maintain the use. Meesters et al. argue that pain assessment tools should be able to measure responsiveness, i.e. being able to detect a decreased pain level following prevision of a pain relieving intervention [57]. Given the lack of a single gold standard tool, most National and International guidelines generally include a list of valid and reliable tools rather than recommend a specific pain assessment tool [1,98,99] and emphasize the importance of the implementation and training process. In a systematic review Dovland Andersen et al. reviewed 12 reviews which in their turn reviewed in all 65 pain scales for non-verbal children, and of which 28 were recommended at least once. The authors concluded that the evidence quality of the reviews was low, and thus their recommendations for what scales to use should be interpreted with caution [100].

As seen in Tables 3–5, there seems to be a sufficient number of instruments for acute and prolonged pain in preterm and term infants. Little is however known about how accurate they are for assessing pain in extremely preterm (before 28 weeks' gestation) or for infants in specific conditions, e.g. undergoing hypothermia. It can also be argued the advantage of instruments that take contextual factors like gestational age into account, e.g. the Premature Infant Pain Profile [79,80].

Table 3
Unidimensional single domain pain instruments. References indicate development and validation publications.

Instrument	Included items	Validated for pain type and age	
ABC scale	Acuteness, rhythmicity and continuity of crying	Acute procedural pain in preterm and term infants	[60,61]
NFCS Neonatal Facial Coding System	Brow bulge, eye squeeze, naso-labial furrow, open lips, horizontal mouth stretch, vertical mouth stretch, lip purse, taut tongue, chin quiver	Acute procedural pain, post-operative pain. A simplified bedside version was published 1998 [62].	[50]

Table 4
Unidimensional multiple domain pain instruments.

Instrument	Included items	Validated for pain type and age	
BIIP Behavioral Indicators of Infant Pain	Behavioral state, brow bulge, eye squeeze, naso-labial furrow, horizontal mouth stretch, taut tongue, finger splay, fisting	Acute procedural pain in preterm and term infants	[53,63]
BPSN Bernese Pain Scale for Neonates	Alertness, duration of crying, time to calm, skin colour, eyebrow bulge with eye squeeze, posture, breathing pattern	Acute procedural pain in preterm and term infants	[64,65]
CHIPPS Children's and Infants' Postoperative Pain Scale	Crying, facial expression, posture of the trunk, posture of the legs, motor restlessness	Post-operative pain in term infants (and children up to 4 years)	[66,67]
COMFORTneo Scale	Alertness, calmness/agitation, respiratory response, crying, body movement, facial tension, body muscle tone. NRS[a] estimate of pain and NRS estimate of distress	Prolonged pain in preterm and term infants. Also validated for sedated infants.	[68]
DAN Douleur Aiguë du Nouveau-né (English name: Acute Pain in Newborns - APN)	Facial expression, limb movement, vocal expression	Acute procedural pain in preterm and term infants	[69]

[a] NRS = Numeric Rating Scale.

8. The use of pain assessment

Many authors have studied the implementation and use of structured pain assessment in clinical practice, and the results are discouraging. A prospective cohort study in 243 neonatal intensive care units from 18 European countries found that only 32% of the 6648 infants received at least one assessment of continuous pain and that only 10% had daily pain assessment [101]. Some countries have come further, e.g. a Dutch study showed that most of the NICU-patients had at least one pain assessment during their hospital stay [7]. The percentage of units which report that they have implemented and are using a structured pain scale varies between countries from 6 to 88% [102–107], and in a survey of neonatal nurses in the USA, 81% reported that their unit used a pain assessment tool regularly [108].

9. How to implement and maintain pain assessment

Despite existence of published clinical guidelines for two decades [1,2] reporting that optimal pain management starts with adequate pain assessment, compliance remains low. Franck and Bruce reviewed the literature and concluded that there is a lack of good-quality evidence for efficacy, effectiveness or cost-benefit of standardized pain assessment tools in relation to pediatric patient or process outcomes [109]. Stevens et al. investigated different knowledge transition (KT) strategies to bridge the gap from pediatric pain research to practice but found that no specific type of single or combination of KT strategies was more effective in improving pain assessment and management outcomes [110].

It has often been said that pain assessment should be the "fifth vital sign" [111] but as such, health care professionals must also know how to interpret the assessment and what action to take. For example, every performed pain assessment should lead to a discussion and decision regarding next steps in clinical decisions to reduce pain, otherwise the assessment merely represents a number on a chart rather than guiding care. The use of a flowchart or algorithm is a helpful tool to ensure that all infants receive adequate pain management, irrespectively who performed the assessment or who has the medical responsibility on that shift [112]. It is also advisable to perform audits or benchmarking on regular basis, to ensure that the unit maintains compliance with the guidelines [113].

10. Novel and future pain assessment

This review focuses on pain assessment methods that are clinically useful in today's neonatal care settings. There are however some interesting novel techniques, or novel applications of known techniques that might be clinically useful in the near future, or that will provide new insights that helps us understand pain assessment better. Many of the methods that focus on brain activity associated with nociception have initially been developed in adult brain research [114] and subsequently been adapted to newborns. In some studies electroencephalography (EEG) has shown noxious-specific activity in term infants [34,115,116], whereas others found no pain-related biobehavioral responses [117]. Near Infrared Spectroscopy (NIRS) measures cerebral hemodynamics by recording oxygenated (HbO2) and deoxygenated (HHb) hemoglobin; an increase in HbO2 and decrease in HHb

Table 5
Multi-dimensional pain instruments.

Instrument	Included items	Validated for pain type and age	
ALPS-Neo Astrid Lindgren and Lund Children's Hospital's Pain and Stress Assessment Scale for Preterm and Sick Newborn Infants	Facial expression, breathing pattern, tone of extremities, hand/foot activity, level of activity	Prolonged pain in preterm and term infants	[70]
CRIES (Acronym of the included items)	Crying, requires oxygen, increased vital signs, expression, sleepless	Prolonged pain in preterm and term infants (and children up to 6 years)	[71,72]
EDIN Échelle Douleur Inconfort Nouveau-né	Facial activity, body movements, quality of sleep, quality of contact with nurses, consolability	Prolonged pain in preterm infants	[73]
NIPS Neonatal Infant Pain Scale	Facial expression, cry, breathing patterns, arms, legs, state of arousal	Acute procedural pain in preterm and term infants	[74,75]
N-PASS Neonatal Pain, Agitation and Sedation Scale	Crying/irritability, behavior state, facial expression, extremities tone, vital signs	Acute procedural pain, prolonged pain (post-operative and during mechanical ventilation) in preterm and term infants	[76]
PAT Pain Assessment Tool	Posture/tone, sleep pattern, expression, colour, cry, respirations, heart rate, oxygen saturation, blood pressure, nurse's perception	Post-operative pain in preterm and term infants	[77,78]
PIPP, PIPP-R Premature Infant Pain Profile (-Revised)	Gestational age, behavioural state, heart rate, oxygen saturation, brow bulge, eye squeeze, naso-labial furrow	Acute procedural pain in preterm and term infants	[79–81]

has been reported to be associated with nociceptive response [33]. NIRS mostly correlates with Premature Infant Pain Profile [118], while it sometimes seems more sensitive than the pain scale [118,119]. Hartley and Slater argue for a composite measure of neonatal pain, combining EEG, NIRS and behavioral/physiological tools [120]. A recent review by Benoit and colleagues examining the methods used to date to assess neurophysiological pain response in infants found that while more methodologically rigorous studies are needed, ERPs derived from EEG appear to hold the greatest promise as indicators of infant nociception during clinical procedures as a means to supplement existing measures [30].

There are other previously studied behavioral, physical, and neurophysiological reactions where modern equipment and advanced computer software may provide a new role in clinical pain assessment. Examples are skin conductance [45,121], heart-rate variability [38,39] and cry analysis [47]. Another promising technique is artificial intelligence/machine learning to analyze large amounts of data from clinical surveillance, laboratory tests and facial expression [122,123].

11. Conclusion

Although we know the importance of pain assessment to ensure optimal pain treatment for newborn infants, health care providers must increase the uptake of valid and reliable pain assessment tools, and also ensure that they are used properly. Researchers need to continue validating existing tools for specific situations or patients like extremely preterm infants or infants treated with hypothermia.

11.1. Practice points

- Pain assessment should be performed on a regular basis with a frequency decided by medical condition and by the previous assessment.
- The result of the pain assessment should be recorded and reported, following an algorithm with specified actions for each level of pain.
- Any unit caring for newborn infants should adopt sufficient pain assessment tools to cover the types of patient they are treating, with the types of pain they are experiencing.

11.2. Research directions

- To develop (when necessary) and validate pain assessment tools for different age groups and medical conditions.
- To gain a deeper understanding on how to measure not only the intensity of pain but also its nature, e.g. duration, type of sensation, localization etc.
- To study the impact of implementing and using a structured pain assessment regime on the medical and developmental outcome.
- Continued examination of optimal implementation and practice uptake related to consistent use of assessment tools and clinical algorithms to guide clinical practice.

Conflicts of interest

Both authors declare that they do not have any conflict of interest.

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