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REVIEW ARTICLE

Defining pain in newborns: need for a uniform taxonomy?

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ABSTRACT

A framework for defining pain terms such as acute, persistent, prolonged or chronic pain to newborns was derived from the scientific literature on neonatal pain assessments, previous attempts to define chronic pain and the clinical and neurophysiological features of neonatal pain. This novel framework incorporates the temporal features, localising characteristics, and secondary effects of the pain experienced, as well as the behavioural and physiological response patterns of newborns.

Conclusion: Although not evidence-based, this framework provides an initial starting point for defining commonly used neonatal pain terms. It will require future revision/refinement based on the accumulating evidence for non-acute pain.

'Ideas need to be fruitful; they do not have to be right. And, curiously enough, the two do not necessarily go together.' (1) Peter W. Nathan, MD, FRCP (1914–2002).

A scientific rationale for pain and its effects in human newborns were first presented thirty years ago (2). Multidisciplinary efforts have since fuelled significant progress in neonatal pain (3), exploring its underlying mechanisms (4,5), describing its epidemiology in clinical settings (6,7), defining its impact on the brain and subsequent development (8,9) or devising clinical assessment and management approaches (10,11). Despite this progress, defining and identifying pain in newborns remains a major challenge. Descriptors such as acute, persistent, prolonged or chronic pain are often used interchangeably for newborns, without clear definitions for these terms. Explicit definitions may help reduce confusion and controversy among clinicians, improve assessment and management and inform study designs in neonatal pain research.

The International Association for the Study of Pain (IASP) defined pain as *'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or* ***described*** *in terms of such damage'* (IASP Committee on Taxonomy, 1969, updated in 1994 and 2002) (12). This definition requires patients to **describe** their pain, by default establishing the primacy of self-report as a 'gold standard'. Although widely accepted across all healthcare professions and biomedical disciplines, this definition lacks applicability to non-verbal populations (13,14) and ignores the cognitive and social dimensions of pain (15). Indeed, pain in newborns was often discounted until the IASP

Key notes

- Neonatal pain assessments are focused mostly on acute pain, whereas prolonged, persistent or chronic pain are relatively ignored; without clear definitions, these terms are often used interchangeably for newborns.
- An initial framework for defining neonatal pain terms is presented, derived from characteristics of the pain experienced, as well as behavioural and physiological response patterns of newborns.
- Explicit definitions of pain terms may facilitate future neonatal pain research and management.

Committee on Taxonomy added a note clarifying that, 'The inability to communicate verbally does not negate the possibility that an individual is experiencing pain' (16).

The question of conscious pain perception in the early preterm newborn (or foetus) has been hotly debated (17–22), mainly because of its social, ethical and legal implications (23–26). Consciousness was widely believed to reside in the cerebral cortex, thus putatively being absent or rudimentary in those without functional thalamocortical connections (20,26), although mechanisms underlying the subcortical control of consciousness (27–29) and functionality of the subplate zone (30–33) appear to challenge that default. Attempting to set forth criteria for early human consciousness would create the difficulties of 'measuring' consciousness and the conundrums of trying to prove or disprove whether consciousness is present at different stages of development (34,35). For the purpose of this review, it is presumed that all viable newborns are capable of consciously perceiving and responding to pain (13,14,36,37).

Given the absence of self-report, pain assessment in newborns is challenging, particularly among ventilated preterm infants with a limited behavioural repertoire. Although numerous pain assessment methods have been devised, validated and implemented in clinical care (38,39), most are focused on the acute, episodic pain resulting from clinically essential, frequently performed invasive procedures. Hartley et al. recently presented an EEG-based measure of nociceptive brain activity evoked by acute noxious stimulation and reduced by a topical anaesthetic (40). This too applies only to acute pain, requires specialised expertise, equipment and analytic capabilities and has a relatively low sensitivity (57%, 64%) and specificity (65%, 68%) to be clinically useful (40).

The need to differentiate acute from prolonged pain was first proposed at the 8th World Congress on Pain (41), and an expert panel later recognised the ability of newborns to experience prolonged/chronic pain (42). To the clinician-researcher, acutely painful events in newborns clearly appeared to cause pain-related distress and could be standardised for research. Clinical examples of prolonged or persistent pain were harder to study—they defied quantification, occurred less frequently, and did not elicit reproducible responses in newborns (43,44). Not surprisingly, therefore, only 10% of newborns in neonatal intensive care units (NICUs) received daily clinical assessments for prolonged, continuous pain (11).

Attempts to define chronic pain in the neonatal context have contributed greatly to our current understanding of pain in infancy (45,46). A few methods to assess the *intensity* of prolonged/chronic pain were devised and validated (Table 1), but given the absence of clear definitions, other aspects specific for chronic pain (duration, periodicity, character or secondary effects) have not been addressed. Despite these gaps, clinicians are using therapies normally reserved for chronic pain in newborns without any clear indications (47–50), or assessment of short-term and long-term risk/benefit ratios. Most clinicians can easily identify examples of *persistent pain* following tissue injury (circumcision, other post-operative pain) or inflammation (necrotizing enterocolitis, pyelonephritis), as well as examples of *chronic pain* (osteogenesis imperfecta, epidermolysis bullosa), but a consensus for developing the taxonomy of pain terms specifically for newborn infants remains elusive (45,46,51).

For adults, various professional societies define acute pain as that associated with tissue injury, whereas chronic pain is defined as pain that extends beyond the period of tissue healing, with levels of pathology insufficient to explain the presence and/or extent of pain. Pain signals may remain active for months or years, causing a 'persistent pain that disrupts sleep and normal living, ceases to have protective functions, and instead degrades health and functional capability'(12,52,53). Turk and Okifuji differentiated acute and chronic pain using criteria for duration and pathology, short-lasting pain with high physical pathology reflects acute pain, whereas prolonged durations with low pathology represent chronic pain (54). However, most chronic pain conditions in adults represent an interplay between significant nociceptive inputs and psychosocial/cognitive factors (55). The 'expected healing period' for defining transitions from acute to chronic pain is variably pegged at one, three or six months (12,52–54,56).

Such time-points clearly exclude newborn infants who have not lived long enough to experience chronic pain, whereas the examples for chronic pain commonly cited by clinicians (e.g. epidermolysis bullosa) usually portend some kind of ongoing tissue pathology (45,46). Also, diseases associated with prolonged pain in newborns (e.g. necrotizing enterocolitis) may have variable and undefined durations of tissue pathology. An empirical approach may be justified therefore, for defining the pain terms commonly used in neonatal care. Putative definitions for acute, prolonged, persistent or chronic pain must be explicit and relevant to the transient newborn period; they must represent the types of pain being experienced, independent of their aetiology or management.

Limited evidence supports management of chronic or persistent pain in neonates, so why do definitions matter at all? We argue that defining an infant's pain would justify a bedside clinician's level of concern, focus their attention towards specific assessment methods and allow them to weigh the risks/benefits of appropriate interventions. Pain definitions will also stimulate further advances to: understand the epidemiology of neonatal pain, investigate the underlying mechanisms at different levels of neurologic maturity, identify biomarkers/patterns for psychophysical or molecular phenotyping, recognise genetic, epigenetic or other factors that place infants at high risk for poor outcomes or long-term complications and lastly, develop targeted therapies for specific types of non-acute pain (15,54). Most clinical trials chose their subjects based on a few selected clinical characteristics, which may or may not match individual newborns with the therapies uniquely suited for their pain. Thus, inclusion criteria incorporating explicit pain definitions may improve homogeneity in

Table 1 Previous studies on persistent or chronic pain in newborns

Authors, Year	Krechel & Bildner, 1995 (86)	Debillon et al., 2001 (93)	Boyle et al., 2006 (43)	Hummel et al., 2008 (87,94)	van Dijk et al., 2009 (95)	Lundqvist et al., 2014 (96)	van Ganzewinkel et al., 2014 (45)
Study design	Observational study	Staff survey, observational study	Staff survey, within an ongoing RCT	Observational study	Observational study	Observational studies, survey	Delphi survey, three rounds
Number of subjects	24	76	22	46	286	86	294
Number of observations	1382	76	89	72	3600	246	525
Age group(s)	32–60 weeks PCA	25–36 weeks GA	23–32 weeks GA	23–40 weeks GA	24–42 weeks GA	23–29 weeks GA	N/A
Male/Female	10/14	N/A	N/A	21/25	174/112	N/A	N/A
Pain assessed	Post-operative	Preterm	Mechanical ventilation	Ventilated or post-operative	Acute procedural	Preterm and sick term	Post-operative or mechanical ventilation
Comparators	Objective Pain Scale	None	NEOPAIN	PIPP	Numeric Rating Scale	None	Likert scale
Assessment method	CRIES Pain Scale	EDIN scale	none	N-PASS	COMFORTneo scale	ALPS-Neo	none
Stimulus studied	Various surgical procedures (VPS placement to PDA closure)	Mechanical ventilation, NEC, surgical closure of PDA	Mechanical ventilation	Mechanical ventilation, various surgical procedures	Not defined	Not defined	Not defined (conditions associated with chronic pain)
Parameters/ Findings	Facial expression (grimace)	Facial activity	Facial expressions	Facial expression	Facial tension	Facial expression	
	Requires oxygen for SpO_2 < 95%	Body movements	Infant activity levels	Extremities, muscle tone	Body movement	Hand/foot activity	Increased energy consumption
	Sleepless	Quality of sleep	Posture/quality of movements	Behaviour state	(body) Muscle tone	Tone of extremities	Hyperalgesia/altered pain perception
	Increased vital signs (BP and HR)	Response to nursing	Response to handling	Changes in vital signs (HR, RR, BP, SpO_2)	Calmness/agitation	Level of activity	Hyperresponsive to all interactions or procedures
	Crying	Consolability	Ventilator dyssynchrony	Crying/irritability	Respiratory response/crying alertness	Breathing pattern	Recurrent or long-lasting pain no proximate event or procedure
Validity	Convergent: R_s = 0.73, p < 0.0001 Discriminant: scores decreased 3.0 pre- vs. post-analgesia, p < 0.0001	Discriminant: scores decreased 4.4 (0.4) pre- vs. post-analgesia, p < 0.0001	N/A	Convergent: R_s = 0.83, p < 0.0001 Discriminant: scores decreased 3.05 pre- vs. post-analgesia, p < 0.0001	Convergent: r = 0.83, p < 0.0001; Discriminant: scores decreased 6.9 pre- vs. post-analgesia, p < 0.001; Sensitivity 81% Specificity 90%	N/A	N/A
Reliability	Inter-rater: R_s=0.72, p < 0.0001	Inter-rater: weighted κ coefficients = 0.59–0.74 (0.69)	N/A	Inter-rater: pain scale ICC 0.95-0.97, p < 0.001; sedation scale ICC 0.9–0.95, p < 0.0001	Inter-rater: weighted κ coefficients = 0.65–0.97 (0.79)	Inter-rater: ICC 0.91 (0.61–0.82 for items)	N/A
Internal consistency	N/A	Cronbach's α coefficient = 0.92	N/A	Cronbach's α coefficient = 0.89	Cronbach's α coefficient = 0.88	Cronbach's α coefficient = 0.95	N/A

ALPS-Neo = Astrid Lindgren's Children's Hospital Pain Scale; BP = Blood pressure; CRIES = Crying, Requires oxygen, Increased vital signs, Expression, Sleepless; EDIN = Échelle Douleur Inconfort Nouveau-Né; GA = Gestational age; HR = Heart rate; ICC = Intraclass correlation coefficient; NEC = Necrotizing enterocolitis; N-PASS = Neonatal Pain, Agitation and Sedation Scale; N/A = not available); PCA = Post-conceptional age; PDA = Patent ductus arteriosus; R_s = Spearman rank correlation coefficient; r = Pearson moment correlation coefficient; RCT = Randomised controlled trial; RR = Respiratory rate; SpO_2 = Peripheral oxygen saturation.

clinical trials. As an initial starting point for defining the different pain terms used for newborns (Table 2), we should consider the following:

Temporal features

Any painful experience is defined by its onset and duration, exemplifying the salient differences between acute and non-acute pain. Acute pain occurs immediately with the onset of tissue injury or stimulation of an inflamed area, and it usually lasts for the duration of the stimulus or for brief periods thereafter (some infants experience a slower decay of pain compared to others). However, the durations assigned for acute, prolonged, persistent or chronic pain are arbitrary at best. In adults, some experts classify pain lasting longer than one month as chronic pain, whereas others consider pain as chronic only if it lasts for longer than three or six months (12,52–54). Similarly, variable criteria are used for children (56,57). Given the temporal characteristics of painful conditions in newborns, the length of the neonatal period, as well as time-courses for developing long-term effects of pain, tolerance to analgesic drugs or other systemic effects, we posit that pain lasting longer than seven days be considered as chronic pain in newborns. This should prompt further diagnostic efforts, re-evaluation of current analgesic strategies, use of alternative therapies and longer-term plans for preventing disability, promoting rehabilitation and restoring function.

Character of pain

For obvious reasons, precise descriptors cannot be chosen for the character of pain (e.g. burning, piercing and shooting) that newborns experience, but clinicians may attempt to discern how well it is localised, or whether it is associated with clear boundaries or not. In the developing nervous system, two features characterise neonatal pain processing: (i) the immature peripheral and central nervous systems are biologically primed towards lower thresholds for activation, excitation and transmission of nociceptive stimuli as compared to older ages; this feature is further accentuated in preterm infants (5,51); (ii) dorsal horn neurons in the spinal cord have large, overlapping cutaneous receptive fields; stimulation of these receptive fields heightens nociceptive signalling and can evoke a long-lasting excitability within the spinal cord (58–60). Indeed, inhibitory signalling in the spinal cord is weak or absent in newborns and develops gradually during infancy (61,62). These features are likely to promote poorer localisation of pain in newborns, while also heightening its secondary effects.

Secondary effects

Tissue injury or inflammation leads to secondary effects such as hyperalgesia (increased pain to a stimulus that is normally painful) and allodynia (pain due to stimuli that do not normally provoke pain). Primary hyperalgesia localises to the area of tissue damage, whereas secondary hyperalgesia occurs in normal areas remote from the site of tissue damage. Despite their biological plausibility (5,61,63,64), limited clinical evidence supports these phenomena in human newborns. Fitzgerald et al. reported primary hyperalgesia following heel lances in newborns and its reversal with topical anaesthetic cream (65), whereas Taddio et al. reported secondary hyperalgesia to venipuncture in one-day-old newborns of diabetic mothers, who had received multiple heel lances for monitoring blood glucose levels (66). Similarly, Andrews et al. reported signs of visceral and somatic hyperalgesia in infants undergoing abdominal surgery (67,68). Allodynia has not been investigated in neonates with prolonged or

Table 2 Suggested starting point for defining the pain terms used for neonatal pain

Pain term	Onset	Duration	Character[a]	Primary hyperalgesia
Acute episodic	Immediate	0–120[b] minutes	Sharp, well-localised	Present, mild, short-lasting
Acute recurrent	Immediate	variable	Sharp, well-localised	Present, moderate or severe
Prolonged[c]	Rapid, may be gradual	One hour to 24[b] hours	Sharp, diffusely localised	Present, moderate or severe
Persistent[c]	Rapid or gradual, cumulative	one to seven days	Dull/sharp, diffusely localised	Present, moderate or severe
Chronic	Usually gradual	Eight days or longer	Dull, diffusely localised	May be present or absent, mild if present

Pain term	Secondary hyperalgesia	Allodynia	Behavioural phenotype	Physiological phenotype
Acute episodic	Probably absent	Probably absent	Strongly reactive and reflexive	High peak, sympathetic activation
Acute recurrent	Present, mild or moderate	Probably absent	Weakly reactive or reflexive	Prolonged peak, sympathetic activation
Prolonged[c]	Mild or absent	Probably absent	Strongly reactive on stimulation	High plateau, sympathetic activation
Persistent[c]	Present, mild or moderate	May be present, mild/moderate	Hyperreactive initially, later hyporeactive	Normal or low sympathetic activation
Chronic	Present, moderate or severe	May be present, moderate/severe	Hyporeactive more often, could also be hyperreactive	Normal or suppressed sympathetic drive

[a]Based on descriptions in adult patients, but may be discerned by a careful physical examination.
[b]Some infants with increased sensitivity to pain may have a slower decay of the acute pain following an invasive procedure, thus justifying some overlap in the durations of acute episodic pain and prolonged pain.
[c]Continuous pain may be characterised as either 'prolonged' or 'persistent'.

persistent pain, although it may be more likely in infants with neurologic impairment (47–50) or in those experiencing opioid withdrawal (69,70). A developmental allodynia appears to exist in preterm neonates (71–75) (but not term neonates (76)), manifesting as similar responses to non-noxious and noxious stimuli. Standardised tests for allodynia need to be developed and performed in newborns with persistent or chronic pain.

Response patterns

The physiological and behavioural responses to acute pain are well characterised in newborns and used for pain assessments (38). Assessment methods developed from models of prolonged or chronic pain also show considerable overlap in the parameters chosen (Table 1), and some of these are different from acute pain (77). In older children, chronic pain is often associated with fatigue, insomnia, impaired cognition or executive function, physical disabilities and mood disturbances (56,57,78). These may be absent or difficult to assess in newborns, particularly among those receiving neonatal intensive care (45,46,51). Behavioural responses generally manifest as 'distress'(38,79), varying in severity and incorporating facial expressions (80), gross body movements (81,82) and subtle movement of hands, fingers or toes (81,83). Physiological responses are incorporated into most assessment scales for acute pain, measuring increased sympathetic activity (38) (and lower parasympathetic tone? (84,85)). Although scales such as CRIES (86) and N-PASS (87) do include changes in vital signs, it is arguable whether neonates facing acute procedural pain versus chronic pain will show similar changes in vital signs. An increased sympathetic drive may not occur in chronic or persistent pain. Heart rate variability, for example, increases during acute pain but is diminished in response to persistent or chronic pain (88,89).

Could the spectrum of rehabilitative interventions used for adult chronic pain be analogous to the behavioural and environmental interventions advocated for newborn care? These include everything from relationship-based models of nursing to management of temperature, light, sound, and circadian rhythms, kangaroo care, sensorial saturation and other interventions (90). As with adults in chronic pain, many drug-based interventions may have unproven benefits and potential harms in newborns. Because of their greater potential for short-term and long-term adverse effects in infants (91,92), we should consider the importance of investigating behavioural and environmental interventions for infant chronic pain as possibly safer than drug therapies (47–50). Although future research will determine novel ways for assessing acute versus non-acute pain in newborns, an empirical framework is proposed to help define various types of neonatal pain. Putative criteria may evolve from this framework, eventually leading to more accurate methods for studying the diverse types of pain experienced by human newborns.

CONFLICT OF INTEREST

The author has no conflicts of interest related to this article.

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