



## SPECIAL ARTICLE

Sedoanalgesia in neonatal units<sup>☆</sup>

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**Abstract** Pain recognition and management continues to be a challenge for health professionals in Neonatal Intensive Care Units. Many of the patients are routinely exposed to repeated painful experiences with demonstrated short- and long-term consequences. Preterm babies are a vulnerable high-risk population. Despite international recommendations, pain remains poorly assessed and managed in many Neonatal Intensive Care Units. Due to there being no general protocol, there is significant variability as regards the guidelines for the approach and treatment of pain between the different Neonatal Intensive Care Units. The objective of this article is to review and assess the general principles of pain in the initial stages of development, its recognition through the use of standardised scales. It also includes its prevention and management with the combination of pharmacological and non-pharmacological measures, as well as to establish recommendations that help alleviate pain in daily clinical practice by optimising pain and stress control in the Neonatal Intensive Care Units.

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**PALABRAS CLAVE**

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**Sedoanalgesia en las unidades neonatales**

**Resumen** El reconocimiento del dolor y su tratamiento en las unidades de cuidados intensivos neonatales continúa siendo un desafío para los profesionales sanitarios responsables de la atención de estos niños. Las exposiciones dolorosas repetidas a las que se someten muchos de estos pacientes de manera rutinaria han demostrado presentar efectos deletéreos a corto y largo plazo. Los recién nacidos prematuros, especialmente vulnerables, suponen una población de alto riesgo. Pese a las recomendaciones internacionales, el dolor sigue siendo evaluado actualmente en muchas ocasiones de manera inconsistente, sin protocolización, siendo patente, además, entre las diferentes unidades de cuidados intensivos neonatales una variabilidad importante en cuanto a las pautas para el abordaje y tratamiento del mismo. El objetivo de este artículo es revisar y valorar los principios generales del dolor en las etapas iniciales del desarrollo, su reconocimiento mediante el uso de escalas protocolizadas, y su prevención y manejo, con la combinación de medidas farmacológicas y no farmacológicas; con el fin de establecer recomendaciones que ayuden a aliviar el dolor en la práctica clínica diaria optimizando el control del dolor y el estrés en las unidades de cuidados intensivos neonatales.

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**Introduction**

As recently as 30 years ago, when newborn infants were subjected to surgical procedures, analgesia was barely used during or after surgery. Today, we not only recognise that newborns experience pain, but its management is considered a principle of good clinical practice. In the usual hospital environment, newborns are routinely subjected to painful procedures from the first moments after birth, such as the intramuscular administration of vitamin K or the prick in the heel for the newborn metabolic screen. Newborns that require intensive care may undergo up to 10–15 painful procedures each day.<sup>1</sup>

The Neonatal Pain Control Group defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage” and stress as “an actual or perceived threat that leads to a disturbance of the dynamic equilibrium between an organism and its environment”, which are both conditions that are ever present in the neonatal intensive care unit (NICU) environment.<sup>2</sup> The concept of comfort develops in close relationship to the definitions of “stress” and “environment”, defined by Kolcaba and DiMarco as a state of relaxation, absence of stress and physiological, emotional and social satisfaction.<sup>3</sup>

The birth process and the subsequent adaptation to extrauterine life are considered stressful experiences, and the separation of mother and infant associated to admission to the NICU has been previously described as noxious.<sup>4</sup> In addition, due to the high complexity of the care delivered in NICUs, these units tend to have bright lights and high noise levels, with an impact on neurodevelopment that has yet to be fully established.<sup>5</sup> Thus, setting up the appropriate environmental conditions to guarantee comfort should be a priority for all the staff involved in the care of these infants.

An increasing number of studies have been focusing on the neurologic impairment that results from overall changes

in the maturation process of the brain, with particular interest on pain as a modifiable risk factor.<sup>6</sup> This particular interest is founded, on one hand, on the increased emphasis on humane care delivery, and on the other on evidence that acute pain produces deleterious effects in the short term and recurrent painful experiences in the early stages of development have long-term deleterious effects.<sup>6,7</sup> Consequently, the assessment, management and prevention of pain are challenges that must be addressed in the NICU setting.

**The physiology of pain**

Pain has been previously described as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. However, this definition has been heavily criticised because it excludes individuals that are not aware of their own bodies or that are unable to express it, and it is important to take into account that pain extends far beyond conventional definitions.

The existing evidence demonstrates that both term and preterm (PT) newborns have the neuroanatomical pathways required for nociception. Traditionally, the prevailing hypothesis has been that perception of pain requires the presence of certain structures connecting the thalamus to the cortex, but other authors have proposed that the spinothalamic tract is sufficient, allowing the subconscious perception of pain.<sup>8</sup>

Nociception most likely becomes possible between weeks 20 and 22 of gestation. Painful stimuli are associated with physiological, hormonal and metabolic markers as early as the week 24. It is at this point in gestation that afferent pathways become fully functional, although the autonomic and neuroendocrine self-regulating systems that modulate sensory experience are still immature (due to the incom-

plete development of the descending inhibitory pathways), which explains the greater vulnerability to pain of PT newborns compared to term infants.<sup>9</sup>

## General measures in pain management

To ensure appropriate pain management in newborns, it is recommended that general measures are established for the purpose in neonatal units:

- Systematic and routine assessment in infants of signs of pain using clinical scales and of its possible causes.
- Minimization or limitation of unnecessary painful stimuli and encouragement of the presence of the parents and their involvement in care delivery.
- Prevention and reduction of acute pain by anticipating the need for analgesia and its timely delivery, including nonpharmacological and pharmacological measures. If the latter are required, analgesic agents should be administered in a stepwise fashion based on the level of pain.
- Standardised protocols/guidelines for pain assessment and management.

## Pain assessment scales

Adequate assessment of pain is essential to guarantee a correct management and treatment of pain. Although there are international guidelines on the subject,<sup>10</sup> there are few protocols specifying the frequency and type of pain assessments that should be performed in everyday clinical practice in Spain.<sup>11</sup>

The verbal expression of the characteristics of pain by the individual is the most suitable approach for determining the nature, location and severity of pain. Since infants are unable to speak, alternative tools had to be developed to correctly identify and assess pain in newborns. Scales to assess pain in newborns are based on the observation and recording of physiological and behavioural changes associated with pain. Their successful application requires considerable training and experience on the part of the observer. Although there are many validated scales, only 5 have exhibited an adequate level of interrater agreement (Table 1).<sup>1,12</sup>

Although none of these scales can be considered ideal, as they are inadequate for assessment of prolonged pain or of newborns who are more premature or with rare clinical conditions, it is nevertheless recommended that each neonatal unit has at least one scale for the assessment of procedural pain and analgesia protocols based on the results of that scale. Due to the subjective nature of the scales and the high level of training required for their correct interpretation, new strategies are required to allow a more objective and accurate assessment of pain. Furthermore, there is evidence that environmental stress in the NICU could influence behavioural responses in newborns. Thus, cortisol responses to painful stimuli in infants experiencing to greater stress levels, while having a greater amplitude, may not be reflected in their behaviour, leading to inaccurate assessments.<sup>13</sup>

There is a growing interest in the role of the cerebral cortex in the neurophysiology of pain and the transmission

of noxious stimuli from nociceptors to the central nervous system, but there are still no conclusive results due to the substantial methodological heterogeneity of studies on the subject.<sup>14</sup> Measurement of skin conductance, based on the response of the sympathetic nervous system to stress, is another of the different technologies that may be useful to measure the response to pain.<sup>15</sup> The same objective has motivated the development of devices that allow the study of the parasympathetic response of the autonomic nervous system to a painful stimulus by measuring changes in heart rate in real time. In both cases, pilot studies have shown promising results, although the available evidence is still insufficient to warrant the widespread introduction of these methods in clinical practice.<sup>16</sup>

## Pain management

### Nonpharmacological measures

These measures seek to promote self-soothing and to alleviate the physiological and behavioural stress caused by acute pain during procedures such as venepuncture. They include breastfeeding, kangaroo care/skin-to-skin contact, containment, non-nutritive sucking, distraction techniques (music, smells, touch, voice...), a quiet environment, soft lighting and sucrose administration. Recently, there has been a growing interest in the presence of the parents during painful procedures.<sup>17</sup> At other ages, the presence of the parents is a commonly used method to reduce anxiety, but in neonatology, the presence of the parents has been introduced as one among many other measures as part of a shift in the approach to neonatal care (open-door policy, kangaroo care, Newborn Individualized Developmental Care and Assessment Program [NIDCAP] etc.) and has only been analysed in relation to pain in a few observational studies, so its independent effect as a pain management measure remains unclear.

Cholecystokinin, a neuropeptide associated with analgesia, is released when newborns are exposed to the familiar odour of the mother, and therefore skin-to-skin contact with the mother may have an analgesic effect.<sup>18</sup>

Although clinical controlled trials have been performed to evaluate each of these measures individually, due to the complexity and heterogeneity of the designs of these studies and, consequently, the low level of evidence that can be gleaned from their results, many of these measures have been underused in clinical practice for a long time. Fortunately, the number of publications in this field is growing and increasing the quality of the evidence supporting their effectiveness, especially when used in combination.<sup>19</sup> Table 2 summarises some of the clinical trials and meta-analyses on the subject published between 2017 and 2020 and the outcomes of the studied interventions.<sup>20–23</sup>

Sucrose administration is the intervention that has been researched most extensively; its use is currently approved by nearly every consensus document and clinical practice guideline.<sup>24</sup> The underlying mechanism of action is not fully understood. It appears that it may involve the release of endogenous opioids, which suggests a potential role of dopaminergic, cholinergic or serotonergic pathways. Sucrose is usually well tolerated, and its administration com-

**Table 1** Pain assessment scales used in newborn infants.

Scale	Type of measurement and items	Score	Indication
Neonatal Facial Cording System Revised (NFCS-R)	- Unidimensional scale - Assesses facial expression. Five items: • Brow bulge • Eyes squeezed shut • Deepening of nasolabial furrow • Horizontal mouth stretch • Tongue protrusion	0–5 Pain: score >3	- Acute pain - Prolonged pain - Postoperative pain
Premature Infant Pain Profile Revised (PIPP-R)	- Multidimensional scale - Behavioural and physiological indicators. Seven items • Change in HR • Decrease in oxygen saturation • Brow bulge • Eye squeeze • Nasolabial furrow • Gestational age • Baseline alertness	0–18 FTNBs 0–21 PTNBs <28 WGA Pain: score >6 Intense pain: $\geq 12$ <i>Requires observation of baseline behaviour before and after painful procedure</i>	- Acute pain - Procedures
Neonatal Pain Agitation and Sedation Scale (N-PASS)	- Multidimensional scale - Independent evaluation of pain and sedation. Five items • Crying/irritability • Baseline state • Facial expression • Muscle tone in upper and lower extremities • Vital signs: HR and oxygen saturation	<i>Pain</i> 0–11 ( $\leq 30$ weeks, 1 additional point) Pain: score $\geq 3$ <i>Sedation</i> , 0 to –10 Deep: –10 to –5 Mild –5 to –2	- Acute/prolonged pain - Procedures in patients under mechanical ventilation - Postoperative pain - Sedation level
Neonatal Infant Pain Scale (NIPS)	- Multidimensional scale Behavioural indicators. Six items • Facial expression • Crying • Breathing pattern • Arm movements • Leg movements • State of arousal	0–7 Items scored on scale of 0–1, except crying, on scale of 0–2 <i>Pain</i> 0–2 no pain/mild pain 3–4 mild-moderate pain >4 severe pain	- Acute pain - Prolonged pain
Bernese Pain Scale Neonates	- Multidimensional scale <i>Two physiological items</i> • Increase in HR • Decrease in oxygen saturation <i>Seven behavioural items</i> • Sleep • Crying (duration) • Soothing • Skin colour • Facial expression • Posture • Breathing pattern	0–27 Pain: score $\geq 11$	- Acute pain

HR, heart rate; FTNB, full term newborn; PTNB, preterm newborn; WGA, weeks of gestational age.

**Table 2** Characteristics of studies conducted in the 2017–2020 period on the combined use of nonpharmacological interventions.

Source (year)	Study design	Population (n)	Painful procedure	Measures	Outcome
Peng et al (2018)	Randomised clinical trial	PTNBs, 29–37 WGA (n = 109)	Heel prick	1. Routine care 2. BF + NNS 3. BF + NNS + containment	Groups 2 and 3: Significant decrease in procedural pain compared to group 1. Group 3: concomitant use of containment decreased the time to recovery.
Gomes et al (2020)	Systematic review and meta-analysis of randomised clinical trials	PTNBs <37 WGA Neonatal pain scale n = 664	ETT aspiration Heel prick	1. Containment 2. Routine care with administration of dextrose during heel prick	Group 1: Significant reduction in pain during ETT aspiration. No difference in heel prick
Liu et al (2017)	Systematic review and meta-analysis of randomised clinical trials	FTNBs and PTNBs 7 trials ≤37 WGA ≤ 2500 g 37–42 WGA ≤ 4000 g (n = 599)	Eye fundus exam Heel prick	1. Sucrose + NNS 2. NNS o sucrose	Group 1: Reduction in pain and duration of crying. No differences in the frequency of bradycardia, tachycardia or desaturation episodes.
Wu et al (2020)	Randomised clinical trial	PTNB, 28–37 WGA (n = 140)	Venepuncture	Sensory stimulation. Four groups 1. Routine care implemented in the unit 2. BM smell or taste 3. BM smell or taste + maternal heartbeat sound 3. BM smell or taste + maternal heartbeat sound + NNS	NBs in group 4 scored lower in the pain assessment scales compared to control group. NBs in groups 2 and 3 scored lower in cases of mild pain compared to the control group. There were no differences between NBs in groups 2 and 3.

BF, breastfeeding; BM, breast milk; ETT, endotracheal tube; FT, full term; NB, newborn; NNS, non-nutritive sucking; PT, preterm; WGA, weeks of gestational age.

**Table 3** Sucrose dose recommended based on gestational age.

Gestational age (weeks)	Sucrose dose (mL)
24–26	0.1
27–31	0.25
32–36	0.5
37–44	1
45–60	2

<sup>a</sup>Due to the lack of conclusive evidence on the maximum cumulative dose and its potential long-term deleterious effects, especially in preterm newborns, administration of more than 10 doses a day is discouraged.

bined with non-nutritive sucking (use of a pacifier/binky) improves its effectiveness. The best outcomes have been observed with administration of sucrose in a 24% solution 2 min before exposure to the painful stimulus, with a duration of the analgesic effect of approximately 4 min. Possible short-term adverse events are rare, sporadic and temporary and include self-limiting episodes of bradycardia or desaturation. Data on the long-term effects are scarce and inconclusive. Previous research on the administration of multiple doses in the first 7–28 days post birth in PT newborns did not find differences in neurologic outcomes in the neonatal period. However, a study by Johnston et al. published in 2007 found that infants that received more than 10 doses in 24 h in the first week of life had the poorest neurodevelopmental outcomes.<sup>25</sup> Although the optimal dosage has yet to be established, the administration of 0.2 to 0.5 mL/kg of 24% sucrose is a widely used strategy.<sup>10</sup> Table 3 presents the recommended doses of sucrose based on gestational age.<sup>26</sup>

Similarly, and with the aim of identifying an effective measure guaranteed to be safe in the long term, other “sweet solutions” must be investigated as alternatives to sucrose. In this regard, we ought to highlight the analgesic effect of the administration of maternal milk. While reviews published to date have not clearly proven the superiority of human milk over sucrose, with similar outcomes in terms of efficacy, harmlessness and multiple other benefits, maternal milk should be considered the first choice. In a recent study that assessed the response of the cerebral cortex to the implementation of different nonpharmacological analgesia strategies, Bembich et al.<sup>27</sup> observed greater activation of the somatosensory and primary motor cortex with the administration of maternal milk (previously extracted or directly from the breast) compared to administration of sucrose, paving the way for future research.

## Pharmacological measures

Pharmacological analgesia is indicated for moderate to severe pain in combination with nonpharmacological measures to optimise outcomes. Analgesics are drugs that are mainly metabolised by the liver and eliminated through the kidneys, with substantial variability between individuals in their distribution and clearance that is even more marked in PT infants.

There are few studies on the safety of these drugs in newborn infants, particularly those born preterm. In animal models, exposure of the immature central nervous system to volatile anaesthetics, benzodiazepines, propofol, barbiturates and ketamine was associated with neurotoxicity. The agonist effect on gamma-aminobutyric acid receptors and antagonist effect on *N*-methyl-D-aspartate receptors of systemic anaesthetics seem to be responsible for the neurodegenerative effect through generalised neuronal apoptosis and impaired synaptogenesis, which in the long term give rise to cognitive and behavioural deficits.<sup>28</sup> However, the few studies that have assessed neurotoxicity in newborns have not yielded conclusive results.<sup>29</sup> In agreement with the findings of animal models, which have shown greater neurodevelopmental impairment in association with a combination of several drugs and prolonged use, neonatal exposure to a single anaesthetic drug and for a short period of time seems safe in healthy individuals,<sup>30,31</sup> although prospective studies are required to assess the impact of repeated doses and prolonged treatment with one or more anaesthetic agents and in the most vulnerable patients, such as PT infants.

The potential neuroprotective effect of dexmedetomidine is the reason why this drug, which as sedative and analgesic effects, has been considered as a possible option for newborns; in foetal and neonatal animal models, its use has not been found to induce neural apoptosis and it has even been associated with a decrease in the neurotoxicity caused by volatile anaesthetics (isoflurane), propofol and ketamine when administered in combination.<sup>32</sup> While clinical trials in newborns need to be performed to assess its neuroprotective effects, the use of dexmedetomidine to date in this population, including PT infants delivered before 28 weeks’ gestation, has been effective and well tolerated in the absence of clinically significant adverse events.<sup>33</sup>

Although in the past it was widely used in newborns, the neurotoxic effects associated with the administration of midazolam in this population (altered level of consciousness, absence of visual tracking, hypertonia, hypotonia, dyskinesia, myoclonus, apnoea, bradycardia), in part secondary to a transient decrease in cerebral perfusion and blood pressure, have led to the current recommendation against its use in PT newborns delivered before 32 weeks’ gestational age. In a Cochrane review of the only 3 randomised controlled trials that compared continuous intravenous infusion of midazolam (20–60 µg/kg/h) with placebo, one of the trials had found a statistically significant increase in the incidence of neurologic adverse events: death, severe intraventricular haemorrhage (grade III-IV) and periventricular leukomalacia.<sup>34</sup>

The neurotoxic effect of opioids, which results from their modulatory effect on neuronal proliferation and apoptosis, has also been described in experimental studies. Similarly, although studies that have assessed the impact of neonatal exposure to opioids on neurodevelopment have yielded heterogeneous results, they, too, suggest that exposure to high doses and prolonged treatment may be associated with adverse outcomes, especially in PT newborns, while the use of these drugs at low doses seemed safe.

The current evidence evinces the need to continue to assess the efficacy, safety and titration of drugs available for use in newborns, as well as to promote their administra-

**Table 4** Clinical trials of drugs used for pain relief in newborns.

Source (year)	Population (n)	Intervention	Results
Ancora et al <sup>35</sup> (2013)	PTNBs <33 wk under IMV; first 72 hpb (N = 131)	<i>Fentanyl</i> at 1 µg/kg IV over 30 min → 1 mcg/kg/h vs placebo Rescue fentanyl (boluses) for invasive procedures or based on pain scales	Due to the absence of evidence on the analgesic effect in case of prolonged pain (EDIN) and increase of adverse outcomes (duration of IMV, delayed passage of meconium), continuous IV infusion of fentanyl is not recommended in PTNBs who are intubated and connected to IMV Administration of IV boluses before invasive procedures or based on pain scales (PIPP), with a decrease in adverse effects relative to continuous infusion
Shin et al <sup>36</sup> (2014)	PTNBs <32 wk under IMV Placement of peripherally inserted central catheter (N = 12)	<i>Remifentanyl</i> at 0.1 µg/kg/min (low dose) vs 0.25 µg/kg/min (high dose)	Analgesic effect only at high doses (PIPP), although with an increase in adverse events (apnoea, bradycardia)
Avino et al <sup>37</sup> (2014)	NBs ≥28 wk Elective or semi-urgent intubation (N = 71)	<i>Remifentanyl</i> at 1 µg/kg IV vs <i>Morphine</i> at 100 µg/kg IV + <i>midazolam</i> at 50 µg/kg IV (both groups given atropine)	Premedication with remifentanyl is at least as effective as morphine + midazolam, with negligible adverse effects
Hünseler et al <sup>38</sup> (2014)	FTNB under IMV > 3 days, given previous sedation/analgesia with fentanyl and midazolam (N = 112)	<i>Clonidine</i> at 1 µg/kg/h vs <i>placebo</i>	Sedative and analgesic effects (Hartwig and COMFORTneo scales), reducing the need for fentanyl/midazolam and withdrawal symptoms, without short-term adverse effects
Valkenburg et al <sup>39</sup> (2015)	PTNBs <3 days under IMV < 8 h (N = 150)	<i>Morphine</i> at 100 µg/kg IV → 10 µg/kg/h vs placebo Rescue morphine (bolus + continuous infusion) as indicated	No evidence of analgesic effect (VAS, NIPS, PIPP) or association with adverse events No differences in the pain threshold, incidence of chronic pain or neurodevelopmental outcomes at 8–9 years
Kabatas et al. <sup>40</sup> (2016)	PTNB <1500 g ROP screening (N = 114)	<i>Paracetamol</i> at 15 mg/kg orally vs placebo	Mild analgesic effect (PIPP)
Roofthoof et al. <sup>41</sup> (2017)	PTNB <32 wk Placement of peripherally inserted central catheter (N = 80)	<i>Paracetamol</i> at dose of 10 vs 15 vs 20 mg/kg IV vs oral sucrose	No evidence of analgesia at any dose or in comparison to sucrose administration (PIPP and COMFORTneo)
Hartley et al <sup>42</sup> (2018)	PTNBs <32 wk or <1501 g → PMA 34–42 wk Heel prick + ROP screening (N = 31)	<i>Morphine</i> at 100 µg/kg orally vs placebo	No evidence of analgesia (PIPP-R), and negative adverse effects (respiratory instability)
Milési et al <sup>43</sup> (2018)	PTNBs <37 wk requiring intubation in the delivery room (N = 60)	<i>Midazolam</i> at 0.2 mg/kg intranasal vs <i>ketamine</i> at 2 mg/kg intranasal (1–2 doses based on pain assessment scale: FANS)	Statistically significant differences in favour of midazolam (0.2–0.4 mg/kg), considered a good option for premedication in the absence of established vascular access
Qiu et al. <sup>44</sup> (2019)	PTNBs <32 wk under IMV; first 72 hpb (N = 53)	<i>Fentanyl</i> at 1 µg/kg IV over 30 min → 1 µg/kg/h vs placebo	Analgesic effect (PIPP) in the first 72 h of IMV and probable neuroprotective effect



Table 4 (Continued)

Source (year)	Population (n)	Intervention	Results
Dekker et al <sup>45</sup> (2019)	PTNB 26–36 <sup>+6</sup> wk MIST (N = 78)	Propofol at 1 mg/kg IV vs placebo	Analgesic effect (COMFORTneo) with a higher incidence of desaturation and need of NIV

FT, full term; hpb, hours post birth; IMV, invasive mechanical ventilation; IV, intravenous; NB, newborn; NIV, non-invasive ventilation; PMA, postmenstrual age; PT, preterm; ROP, retinopathy of prematurity; wk, weeks.

Pain assessment scales: EDIN, Echelle Douleur Inconfort Nouveau-N; FANS, 'Faceless' Acute Neonatal pain Scale; NIPS, Neonatal Infant Pain Profile; PIPP, Premature Infant Pain Profile; PIPP-R, Premature Infant Pain Profile-Revised; VAS, Visual Analog Scale.

tion in combination with nonpharmacological measures with the aim of using the minimum effective dose and minimise adverse events. Table 4 presents the clinical trials of drugs used for pain relief in newborns conducted in the 2014–2020 period.<sup>35–45</sup>

There is substantial variability in the use of pharmacological measures for pain management between NICUs, both

in Spain and at the international level,<sup>46</sup> and there are no established protocols or consensus guidelines on the subject. Although in recent years measures for the prevention and treatment of procedural pain have been widely implemented in neonatal units, the use of sedation or analgesia in subacute or chronic care interventions, such as invasive mechanical ventilation, remains controversial.<sup>35</sup>

Table 5 Sedation and analgesia in specific situations/procedures.

Procedure	Intervention
Heel prick	<ul style="list-style-type: none"> <li>• Consider venepuncture in late PTNBs and FTNBs (less painful and more effective).</li> <li>• Sucking with BF or sucrose 2 min before</li> <li>• Swaddling and containment vs kangaroo care</li> <li>• Use of spring-loaded lancet</li> </ul>
Venous blood draw/placement of venous catheter	<ul style="list-style-type: none"> <li>• Sucking with BF or sucrose 2 min before</li> <li>• Swaddling and holding</li> <li>• Topical anaesthetic (EMLA<sup>®</sup>)</li> </ul>
Arterial blood draw/placement of arterial catheter	<ul style="list-style-type: none"> <li>• Sucking with BF or sucrose 2 min before</li> <li>• Swaddling and holding</li> <li>• Topical anaesthetic (EMLA<sup>®</sup>)</li> </ul>
Central line placement	<ul style="list-style-type: none"> <li>• Consider Subcutaneous infiltration of lidocaine</li> <li>• Nonpharmacological measures</li> <li>• Topical anaesthetic (EMLA<sup>®</sup>)</li> <li>• Consider subcutaneous infiltration of lidocaine</li> </ul>
Umbilical catheter placement	<ul style="list-style-type: none"> <li>• Consider general anaesthesia: analgesia with rapid-onset opioids ± sedation</li> <li>• Nonpharmacological measures</li> </ul>
Peripherally inserted central line placement	<ul style="list-style-type: none"> <li>• Avoid skin suturing or haemostatic techniques</li> <li>• Nonpharmacological measures</li> <li>• Topical anaesthetic (EMLA<sup>®</sup>)</li> </ul>
Lumbar puncture	<ul style="list-style-type: none"> <li>• Consider single dose of rapid-onset opioid for pain management (slow infusion)</li> <li>• Sucking with BF or sucrose 2 min before</li> <li>• Positioning and careful holding</li> <li>• Topical anaesthetic (EMLA<sup>®</sup>)</li> <li>• Consider Subcutaneous infiltration of lidocaine</li> <li>• Consider single dose of rapid-onset opioid for pain management in intubated patients</li> </ul>
Subcutaneous/intramuscular injection	<ul style="list-style-type: none"> <li>• Avoid this route of administration and replace with IV delivery</li> <li>• Nonpharmacological measures</li> </ul>
Tracheal intubation	<ul style="list-style-type: none"> <li>• Consider Topical anaesthetic (EMLA<sup>®</sup>)</li> <li>• Nonpharmacological measures</li> <li>• Premedication recommended except in case of urgent intubation, although there is no established first-line combination: <ul style="list-style-type: none"> <li>-Administration of rapid-onset analgesic ± hypnotic/sedative agent</li> <li>-Delivery of short-acting muscle relaxant by experienced personnel recommended except in nonvigorous patients, including extreme PTNBs</li> <li>-Atropine (0,01–0,02 mg/kg)</li> </ul> </li> </ul>



Table 5 (Continued)

Procedure	Intervention
Surfactant administration (LISA/MIST)	<ul style="list-style-type: none"> <li>• Sucking with BF or sucrose 2 min before</li> <li>• Swaddling and holding</li> <li>• Consider premedication: rapid-onset short-acting drug (fentanyl, propofol)<sup>a</sup></li> </ul>
ETT aspiration	<p>Nonpharmacological measures.</p> <p>Short aspirations, limiting depth of insertion to ETT tip</p> <p>Consider low dose of rapid-onset opioid.</p>
Mechanical ventilation	<ul style="list-style-type: none"> <li>• Nonpharmacological measures</li> <li>• Insufficient evidence to recommend routine use of sedation-analgesia</li> <li>• Anticipated short duration and/or SDR associated with prematurity: intermittent infusion of opioids before invasive procedures (minimum effective dose to achieve adequate pain relief based on use of validated scales)</li> <li>• Anticipated long duration in FTNB/PTNB with severe respiratory failure: consider continuous infusion of opioids with dose titration ± benzodiazepine in case of pulmonary hypertension (not recommended in PTNBs)</li> </ul>
Chest tube placement	<ul style="list-style-type: none"> <li>• Nonpharmacological measures</li> <li>• Consider Subcutaneous infiltration of lidocaine</li> <li>• Consider single dose of rapid-onset opioid for pain relief ± sedative</li> </ul>
Orogastric/nasogastric tube placement	<ul style="list-style-type: none"> <li>• Nonpharmacological measures</li> <li>• Use lubricant and attempt rapid insertion</li> </ul>
Urinary catheter placement	<ul style="list-style-type: none"> <li>• Nonpharmacological measures</li> <li>• Sterile lubricating gel</li> </ul>
Eye fundus examination	<ul style="list-style-type: none"> <li>• Nonpharmacological measures</li> </ul>
Active hypothermia	<ul style="list-style-type: none"> <li>• Nonpharmacological measures</li> <li>• Consider opioids at low doses (decreased liver and kidney metabolism associated with asphyxia) and <math>\alpha</math>-2 adrenergic agonists</li> </ul>
Removal of catheter or chest tube	<ul style="list-style-type: none"> <li>• Nonpharmacological measures</li> </ul>

BF, breastfeeding; EMLA<sup>®</sup>, lidocaine + prilocaine; ETT, endotracheal tube; FTNB, full term newborn; LISA, less invasive surfactant administration; MIST, minimally invasive surfactant therapy; PTNB, preterm newborn; RDS, respiratory distress syndrome.

EMLA<sup>®</sup>: up to 1 g and 10 cm<sup>2</sup> over 1 h, single dose in 24 h. Although the summary of product characteristics does not recommend its use in PTNBs (<37 weeks) due to the risk of methaemoglobinaemia, the only clinical trial that assessed the safety of EMLA<sup>®</sup> versus placebo in PTNB delivered at 30–36 weeks' gestation did not find clinically significant levels of methaemoglobin (>5%) in any of the patients.<sup>47</sup>

<sup>a</sup> At present, there is no consensus on premedication due to the absence of a drug with a predictable pharmacokinetic profile that allows maintenance of spontaneous breathing, thereby preventing certain short- and long-term adverse effects, although new studies are required to investigate the ideal sedation and analgesia scheme to achieve an adequate balance between the maintenance spontaneous breathing and the treatment of pain associated with surfactant administration.<sup>48</sup>

Table 5 provides recommendations on the pharmacological and nonpharmacological pain relief measures to use in the most frequent situations and procedures in neonatal clinical practice.<sup>47,48</sup>

## Conclusions

The assessment of pain needs to be standardised and become a routine practice in neonatal units to optimise pain relief, if pain cannot be avoided, through the combination of pharmacological and nonpharmacological measures, titrating drugs to the minimum effective dose and minimising potential adverse events. Randomised controlled trials need to be developed to assess the short- and long-term impact of exposure to the sedatives and analgesics that are currently available and to establish protocols for the management of stress and pain in the neonatal population. Research in neuroprotection could facilitate adequate pain management in these patients while protecting the developing brain.

## Conflicts of interest

The authors have no conflicts of interest to declare.

## References

1. Carbajal R, Rousset A, Danan C, Coquery S, Nolent P, Ducrocq S, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. *JAMA*. 2008;300:60–70.
2. Anand KJ, Aranda JV, Berde CB, Buckman S, Capparelli EV, Carlo W, et al. Summary proceedings from the neonatal pain-control group. *Pediatrics*. 2006;117:S9–22.
3. Kolcaba K, DiMarco M. Comfort theory and its application to pediatric nursing. *Pediatr Nurs*. 2005;31:187–94.
4. Shonkoff JP, Garner AS, Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, Section on Developmental and Behavioral Pediatrics. The lifelong effects of early childhood adversity and toxic stress. *Pediatrics*. 2012;129:e232–46.
5. Cheong JLY, Burnett AC, Treyvaud K, Spittle AJ. Early environment and long-term outcomes of preterm infants. *J Neural Transm (Vienna)*. 2020;127:1–8.

6. McPherson C, Miller SP, El-Dib M, Massaro AN, Inder TE. The influence of pain, agitation, and their management on the immature brain. *Pediatr Res.* 2020;88:168–75.
7. Vinal J, Grunau RE. Impact of repeated procedural pain-related stress in infants born very preterm. *Pediatr Res.* 2014;75:584–7.
8. Bellieni CV. New insights into fetal pain. *Semin Fetal Neonatal Med.* 2019;24:101001.
9. Maxwell LG, Fraga MV, Malavolta CP. Assessment of pain in the newborn: an update. *Clin Perinatol.* 2019;46:693–707.
10. Committee on fetus and newborn and section on Anesthesiology and Pain Medicine. Prevention and management of procedural pain in neonates: an update. *Pediatrics.* 2016;137:e20154271.
11. Avila-Alvarez A, Carbajal R, Courtois E, Pertega-Diaz S, Anand KJ, Muñoz-García J, Grupo español del proyecto Europain. Clinical assessment of pain in Spanish neonatal intensive care units. *An Pediatr (Barc).* 2016;85:181–8.
12. Kappesser J, Kamper-Fuhrmann E, de Laffolie J, Faas D, Ehrhardt H, Franck LS, et al. Pain-specific reactions or indicators of a general stress response?: Investigating the discriminant validity of 5 well-established neonatal pain assessment tools. *Clin J Pain.* 2019;35:101–10.
13. Jones L, Fabrizi L, Laudiano-Dray M, Kimberley Whitehead K, Meek J, Verriotis M, et al. Nociceptive cortical activity is dissociated from nociceptive behavior in newborn human infants under stress. *Curr Biol.* 2017;27:3846–51.
14. Benoit B, Martin-Misener R, Newman A, Latimer M, Campbell-Yeo M. Neurophysiological assessment of acute pain in infants: a scoping review of research methods. *Acta Paediatr.* 2017;106:1053–66.
15. Hu J, Modanloo S, Squires JE, Harrold J, Harrison D. The validity of skin conductance for assessing acute pain in infants: a scoping review. *Clin J Pain.* 2019;35:713–24.
16. Cremillieux C, Makhlof A, Pichot V, Trombert B, Patural H. Objective assessment of induced acute pain in neonatology with the newborn infant parasympathetic evaluation index. *Eur J Pain.* 2018;22:1071–9.
17. Mc Nair, Campbell-Yeo M, Johnston C, Taddio A. Non pharmacologic management of pain during needle puncture procedures in infants: current research evidence and practical considerations: an update. *Clin Perinatol.* 2019;46:709–30.
18. Hebb AL, Poulin JF, Roach SP, Zacharko RM, Drolet G. Cholecystokinin and endogenous opioid peptides: Interactive influence on pain, cognition, and emotion. *Prog Neuropsychopharmacol Biol Psychiatry.* 2005;29:1225–38.
19. Lago P, Garetti E, Bellieni CV, Merazzi D, Levet PS, Ancora G, et al. Systematic review of nonpharmacological analgesic interventions for common needle-related procedure in newborn infants and development of evidence-based clinical guidelines. *Acta Paediatr.* 2017;106:864–70.
20. Peng HF, Yin T, Yang L, Wang C, Chang YC, Jeng MJ, et al. Non-nutritive sucking, oral breast milk, and facilitated tucking relieve preterm infant pain during heel-stick procedures: A prospective, randomized controlled trial. *Int J Nurs Stud.* 2018;77:162–70.
21. Gomes Neto M, Lopes SA, Morais Araujo AC, Silva Oliveira L, Bernardone Saquetto M. The effect of facilitated tucking position during painful procedure in pain management of preterm infants in Neonatal Intensive Care Unit: a systematic review and meta-analysis. *Eur J Pediatr.* 2020;179:699–709.
22. Liu Y, Huang X, Luo B, Peng W. Effects of combined oral sucrose and nonnutritive sucking (NNS) on procedural pain of NICU newborns, 2001 to 2016: a PRISMA-compliant Systematic Review and Meta-Analysis. *Medicine (Baltimore).* 2017;96:e6108.
23. Wu HP, Yin T, Hsieh KH, Lan HY, Feng RC, Chang YC, et al. Integration of different sensory interventions from mother's breast milk for preterm infant pain during peripheral venipuncture procedures: a prospective randomized controlled trial. *J Nurs Scholarsh.* 2020;52:75–84.
24. Stevens B, Yamada J, Ohlsson A, Haliburton S, Shorkey A. Sucrose for analgesia in newborns infants undergoing painful procedures. *Cochrane Database Syst Rev.* 2016;7:CD001069.
25. Johnston C, Filion F, Snider L, Limperopoulos C, Majnemer A, Pelousa E, et al. How much sucrose is too much sucrose? *Pediatrics.* 2007;119:226.
26. Kanwaljeet Anand JS, Available from: <https://www.uptodate.com/contents/prevention-and-treatment-of-neonatal-pain>, 2019.
27. Bembich S, Cont G, Causin E, Paviotti G, Marzari P, Demarini S. Infant analgesia with a combination of breast milk, glucose, or maternal holding. *Pediatrics.* 2018;142:e20173416.
28. Montana MC, Evers AS. Anesthetic neurotoxicity: new findings and future directions. *J Pediatr.* 2017;181:279–85.
29. Lin EP, Lee JR, Lee CS, Deng M, Loepke AW. Do anesthetics harm the developing human brain? An integrative analysis of animal and human studies. *Neurotoxicol Teratol.* 2017;60:117–28.
30. Sun LS, Li G, Miller TLK, Salorio C, Byrne MW, Bellinger DC, et al. Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. *JAMA.* 2016;315:2312–20.
31. McCann ME, de Graff JC, Dorris L, Disma N, Withington D, Bell G, et al. Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicenter, randomised controlled equivalence trial. *Lancet.* 2019;393:664–77.
32. Andropoulos DB. Effect of anesthesia on the developing brain: infant and fetus. *Fetal Diagn Ther.* 2018;43:1–11.
33. Chrysostomou C, Schulman SR, Herrera-Castellanos M, Cofer BE, Mitra S, García da Rocha M, et al. A phase II/III, multicenter, safety, efficacy, and pharmacokinetic study of dexmedetomidine in preterm and term neonates. *J Pediatr.* 2014;164:276–82.
34. Ng\_E, Taddio\_A, Ohlsson\_A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. *Cochrane Database Syst Rev.* 2012;6. CD002052.
35. Ancora G, Lago P, Garetti E, Pirelli A, Merazzi D, Mastrocola M, et al. Efficacy and safety of continuous infusion of fentanyl for pain control in preterm newborns on mechanical ventilation. *J Pediatr.* 2013;163:645–51.
36. Shin SH, Kim HS, Lee J, Choi KY, Lee JH, Kim EK, et al. A comparative study of two remifentanyl doses for procedural pain in ventilated preterm infants: a randomized, controlled study. *Pediatr Crit Care Med.* 2014;15:451–5.
37. Avino D, Zhang WH, de Villé A, Johansson AB. Remifentanyl versus morphine-midazolam premedication on the quality of endotracheal intubation in neonates: a noninferiority randomized trial. *J Pediatr.* 2014;164:1032–7.
38. Hünsele C, Balling G, Röhlig C, Blickheuser R, Trieschmann U, Lieser U, et al. Continuous infusion of clonidine in ventilated newborns and infants: a randomized controlled trial. *Pediatr Crit Care Med.* 2014;15:511–22.
39. Valkenburg AJ, van den Bosch GE, de Graaf J, van Lingen RA, Weisglas-Kuperus N, van Rosmalen J. Long-term effects of neonatal morphine infusion on pain sensitivity: follow-up of a randomized controlled trial. *J Pain.* 2015;16:926–33.
40. Kabatas EU, Dursun A, Beken S, Dilli D, Zenciroglu A, Okumus N. Efficacy of single dose oral paracetamol in reducing pain during examination for retinopathy of prematurity: a blinded randomized controlled trial. *Indian J Pediatr.* 2016;83:22–6.
41. Roofthoof D, Simons S, van Lingen RA, Tibboel D, van den Anker J, Reiss I. Randomized controlled trial comparing different single doses of intravenous paracetamol for placement of peripherally inserted central catheters in preterm infants. *Neonatology.* 2017;112:150–8.
42. Hartley C, Moultrie F, Hoskin A, Green G, Monk V, Bell J. Analgesic efficacy and safety of morphine in the Procedural Pain in Premature Infants (Poppi) study: randomised placebo-controlled trial. *Lancet.* 2018;392:2595–605.

43. Milési C, Baleine J, Mura T, Benito-Castro F, Ferragu F, Thiriez G. Nasal midazolam vs ketamine for neonatal intubation in the delivery room: a randomised trial. *Arch Dis Child Fetal Neonatal Ed.* 2018;103:F221–6.
44. Qiu J, Zhao L, Yang Y, Zhang JH, Feng Y, Cheng R. Effects of fentanyl for pain control and neuroprotection in very preterm newborns on mechanical ventilation. *J Matern Fetal Neonatal Med.* 2019;32:3734–40.
45. Dekker J, Lopriore E, van Zanten HA, Tan RNGB, Hooper SB, Te Pas AB. Sedation during minimal invasive surfactant therapy: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed.* 2019;104:F378–83.
46. Carbajal R, Eriksson M, Courtois E, Boyle E, Avila-Alvarez A, Andersen RD. Sedation and analgesia practices in neonatal intensive care units (EUROPAIN): results from a prospective cohort study. *Lancet Respir Med.* 2015;3:796–812.
47. Foster JP, Taylor C, Spence K. Topical anaesthesia for needle-related pain in newborn infants. *Cochrane Database Syst Rev.* 2017;2. CD010331.
48. Vento M, Bohlin K, Herting E, Roehr CC, Dargaville PA. Surfactant administration via thin catheter: a practical guide. *Neonatology.* 2019;116:211–26.