Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria

Submitted on: 03/22/2019
Approved on: 04/01/2019

ORIGINAL ARTICLE

Themed article

Evaluation and treatment of pain in the neonatal period

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Keywords:
Infant,
Pain,
Analgesia.

Abstract

Based on the knowledge that newborns, even the extremely preterm and critically ill of any gestational age, are able to experience pain and that pain in these patients leads to physiological and behavioral repercussions that may increase morbidity and the mortality in the short and medium term and that can lead to consequences in the development of the nociceptive and neurological system in the long term, the presence of pain in newborns hospitalized in intensive care unit or submitted to potentially painful procedures must be systematically evaluated and, when present, treated according to the state of the art with regard to pharmacological and non-pharmacological measures for pain relief in the neonatal period. This article is a practical guide to the systematic evaluation of pain in the newborn and its treatment. It is evident that, in the case of a subjective symptom in a population that is not yet able to verbalize what it feels and for which the scientific evidence on which the therapeutic measures are based is scarce, the controversy permeates the whole theme. Thus, the reader will find, far from an absolute truth, a suggestion for his practical performance.

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INTRODUCTION

In the past 40 years, several studies have shown that:

- Newborns, even preterm infants, are neurobiologically apt to feel pain;
- Newborns exposed to intense or prolonged pain have increased morbidity;
- Lack of behavioral response to painful stimuli does not mean absence of pain;
- To evaluate and reduce pain in the neonate, validated instruments must be used consistently throughout the analgesia period;
- One of the major hurdles to the treatment of pain in the neonatal period is the difficulty of assessing pain in this population.

Recognizing, evaluating and treating pain are important aspects of a day-to-day neonatal intensive care unit (NICU) job, as pain often accompanies various invasive therapies and procedures used to save the lives of these patients. Despite this, the use of pain relief measures for potentially painful procedures still occurs in a heterogeneous and sometimes even scarce manner in NICUs. In Europe, a multicenter prospective cohort involving 18 countries, 243 neonatal units and 6,680 neonates, found that the use of analgesia ranged from 0% to 100% among the 243 centers. In the same line, a multicenter study performed in four Brazilian university neonatal units, in the years 2001, 2006 and 2011, reported an increase in the use of analgesics for painful procedures during the study years. However, in 2011 the frequency of analgesia administration remained very low, being present in 36% for lumbar puncture; 30% for intubation; 48% for mechanical ventilation and 89% for the first three postoperative days.

One of the most cited causes for pain undertreatment in the neonatal period is the gap between scientific knowledge and clinical practice approach, as well as the difficulty of assessing pain in the pre-verbal infant. Pain assessment in the neonatal population is not an easy task, since the subjective nature of painful experience and the existence of a few reliable, valid and clinically applicable instruments to measure the presence and intensity of pain are difficult to transpose barriers.

More than 40 pain assessment scales have been described in the literature to evaluate pain in the neonatal period, and there is no gold standard instrument yet. Given the diversity of existing scales, several authors suggest that the neonatal units should define a practical guide for the evaluation of pain in the neonatal period, maintaining a practical and frequent training of the neonatal multidisciplinary team. The following paper, far from being the only truth, is a suggestion of a guideline to be followed at the bedside.

PAIN ASSESSMENT

NURSING TEAM: should employ the neonatal pain, agitation, and sedation assessment scale - Neonatal Pain, Agitation and Sedation Scale (N-PASS; Chart 1) simultaneously with the monitoring of vital signs, i.e. every one to three hours, according to the pain severity. Scores > 3 should alert to the need for analgesics' introduction or dose adjustment.

OPERATIONAL SETTINGS FOR N-PASS APPLICATION

Sedation Evaluation:

- Sedation is scored from 0 to -2 for each physiological and behavioral criterion, so they are summed and scored as a negative score (from 0 to -10).

Chart 1. N-PASS - Neonatal Pain, Agitation and Sedation Scale (Hummel et al, 2009).

	Sedation		Sedation/Pain	Pain/Agitation	
	-2	-1	0/0	1	2
Crying/ Irritability	No cry with painful stimuli	Moans or cries minimally with painful stimuli	No sedation / no pain signs	Irritable or consolable crying at intervals	High-pitched or silent-continuous inconsolable cry
Behavior State	No arousal to any stimuli No spontaneous movement	Arouses minimally with painful stimuli Little spontaneous movement	No sedation / No pain signs	Restless, squirming Awakens frequently, se contorts. Wakes up frequently	Arching, kicking Constantly awake or Arouses minimally / no movement (not sedated)
Extremities Tone	Mouth is lax No expression	Minimal expression. With stimuli	No sedation / no pain signs	Any pain expression intermittent	Any pain expression Continual
Extremities Tone	No grasp reflex Flaccid tone	Weak grasp reflex Low muscle tone	No sedation / pain signs	Intermittent clenched toes, fists or finger splay Body is not tense	Continual clenched toes, fists or finger splay Body is tense
Vital Signs HR, RR, BP, SaO_2	No variability with stimuli Hypoventilation or apnea	< 10% variability from baseline with stimuli	No sedation / No Pain signs	↑ 10-20% from baseline $SatO_2$ 76-85% with stimulation; quick recovery	↑ 20% from baseline SaO_2 < 75% with stimulation Slow recovery Out of sync/fighting vent

Sedation: -10 to 0 Deep Sedation: -10 to -5 and Mild: -5 to -2.
Pain: 0-11 (add 1 point if NB < 30 weeks of corrected GA). With Pain score >3.

- The "zero" score is given to the newborn who has no signs of sedation and is reactive.

• Desired levels of sedation vary according to the situation:

- "Deep sedation" score from -10 to -5
- "Mild sedation" score from -5 to -2
- Deep sedation is not recommended unless the neonate is on mechanical ventilation because of the high potential for hypoventilation and apnea.

• Negative score without administration of opioids/sedatives may indicate:

- Prolonged or persistent response to premenstrual pain/stress
- Neurological depression, sepsis or other pathologies.

PAIN/AGITATION ASSESSMENT

Pain should be included in the assessment of vital signs.

• Pain is scored from 0 to +2 for each behavioral and physiological criterion and then summed.

- Points are added to the assessment of pain in premature newborns based on gestational age to compensate for the limited capacity of behavioral expression of pain in this group;
- The total score is documented with positive numbers (0 to +10).
- Treatment/Interventions are suggested in cases of scores > 3 or in front of well-known interventions and/or stimuli.

• The goal of pain treatment/intervention is to keep score ≤ 3.

• Most frequent indications for pain assessment:

SCORING CRITERIA

A) Irritability/Crying

-2: Does not respond to painful stimuli: does not cry with needle stick or does not respond to of upper airways aspiration, endotracheal cannula or does not respond to general care provided

-1: Groans, sighs or crying (audible or silent) with painful stimuli.

0: No signs of sedation or pain/agitation.

+1: Child irritated or crying intermittently, and allows to be comforted.

+2: Any of the following criteria: continuous or inconsolable loud or silent crying or, if intubated, continuous silent crying.

B) Behavioral Status

-2: Does not arouse or react to any stimulus, with continuously open or closed eyes and absence of spontaneous movements

-1: Minimal spontaneous, brief and/or minimal movements to any stimulus, that is, briefly opens the eyes or reacts when aspirated or presents withdrawal reflex to painful stimuli.

0: No signs of sedation or pain/agitation

+1: Any of the following: restless and wriggles or wakes up frequently and/or easily with minimal or absent stimuli

+2: Any of the following: kicks, hyperextends chest and limbs; is constantly awake or does not show any minimal movement or excitement after stimulation (not sedated, has no inadequate gestational age or clinical situation to justify).

C) Facial Expression (Figure 1):

-2: Any of the following elements: relaxed mouth, drooling or absence of facial expression, at rest or with stimuli.

-1: Minimum facial expression with stimulus

0: No signs of sedation or pain/agitation

+1: Any facial expression seen intermittently: look if the eyebrows are arched and joined, if the forehead is protruding, if the eyes are squeezed, if the nostrils are abated and enlarged; if the cheeks are raised and/or if the nasolabial groove is deepened.

+2: Any continuous facial expression: look if the eyebrows are arched and joined, if the forehead is protruding, if the eyes are squeezed, if the nostrils are abated and enlarged; if the cheeks are raised and/or if the nasolabial groove is deepened.

D) Limbs' tonus

-2: Any of the following criteria: no palmar or plantar grip and/or sagging

-1: Any of the following criteria: poor palmar or plantar grip and/or decreased tonus

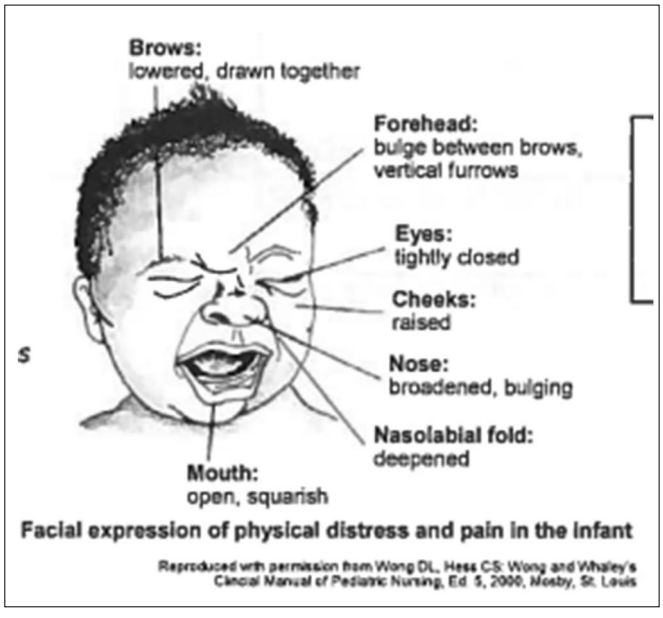

Figure 1. Distress and pain in the infant.

0: No signs of sedation or pain/agitation

+1: Hands closed or intermittently flat (<30s duration) and the body is not tense

+2: Any of the following criteria: hands closed or intermittently flat (> 30s duration) or body is tense/rigid.

E) Vital Signs: HR, BP, RR and O2 Saturation

-2: Any of the following criteria: no vital sign changes, hypoventilation or apnea, or neonate in ventilation - absence of spontaneous breathing.

-1: Vital signs with little variability with stimulus - less than 10% of initial value.

0: No signs of sedation or pain/agitation.

+1: Any of the following criteria: HR, RR and/or BP 10-20% above initial values or, during care or stimulation procedures, decrease from minimal to moderate saturation (SatO2 76-85%) and rapid recovery (<2 minutes).

+2: Any of the following criteria: HR, RR and/or BP > 20% above initial values or, during care or stimulation procedures, there is a significant drop in O2 saturation (SatO2 <75%) and slow recovery (> 2 minutes) or asynchronous ventilation, with "fight" with the ventilator.

MEDICAL TEAM: consider using the N-PASS scale (Chart 1) in the following situations: N-PASS score higher than 3, according to the nursing team's assessment; newborns submitted to surgery of any kind, thoracic drainage, tracheal intubation and mechanical ventilation, phlebotomy and/or percutaneous catheter insertion; bone fractures; patients with necrotizing enterocolitis and in every neonate <1000g. The frequency of pain assessments in the newborn should follow that described on Chart 2.

PAIN PREVENTION IN THE NEWBORN

It is imperative that neonatal units organize themselves to minimize the pain of their patients:

- NB Light exposure reduction, with the use of a bulkhead in the incubator.
- Decreased noise levels in the intensive care units.
- Minimal intervention, that is, performing potentially painful or uncomfortable procedures together, allowing rest periods to the patient.
- Blood collections should be grouped and the use of central catheters stimulated.
- Use a small amount of adhesive tape when attaching venous/arterial catheters, tracheal cannulae and thoracic drains, among others.
- The procedures should preferably be performed by the most qualified physician and/or nurse in the unit or under their direct supervision.
- Prioritize the patient's contact with the parents to stimulate the newborn's well-being.

ANALGESIA INDICATIONS IN THE NEWBORN

The main indications for analgesia in the neonatal period are below. However, one should remember that there are no absolute indications for the use of analgesics in the newborn. The decision regarding pain relief should always be individualized. It is important to consider the presence of pain and the therapeutic need in:

- Patients with necrotizing enterocolitis;
- Newborns with neonatal birth injuries, such as fractures or lacerations;
- NB facing painful procedures such as thoracic drainage, elective tracheal intubation, catheter insertion, cerebrospinal fluid puncture, multiple arterial, venous and/or capillary punctures;
- Surgical procedures of any kind;
- Intubated patients under mechanical ventilation;
- Any seriously ill neonate who may need multiple painful procedures.

Chart 2. Pain assessment frequency in the neonatal unit.

Clinical situation	Interval between assessments	Total assessment period
1º PO (any surgery)	4/4	24
After the 1st PO		
Large surgeries	6/6	96
Small surgeries	8/8	48
Thorax drainage	8/8	While present
Tracheal intubation and mechanical ventilation	8/8	While present
Phlebotomy and/or percutaneous catheter	8/8	24
Bone fractures	8/8	72
Necrotizing enterocolitis	8/8	During the acute phase
NB smaller than 1000g	6/6	1st week of life

It is recommended to start or adjust analgesia whenever the N-PASS score exceeds three.

NON-PHARMACOLOGICAL PAIN TREATMENT

SKIN-TO-SKIN CONTACT: this may be recommended in healthy newborns who require an isolated painful procedure, such as capillary or venous puncture or intramuscular injection. Skin-to-skin contact is recommended for at least 2 minutes prior to the procedure. Its use as an analgesic measure in neonates with birth weight <1000 g has an unknown efficacy.

NON-NUTRITIONAL SUCTION: analgesia promoted by non-nutritional sucking occurs only during rhythmic suction movements; however, its analgesic efficacy is not known in critically ill/extremely immature infants and subjected to multiple and repeated painful stimuli. This therapeutic approach can be applied to the newborn during the performance of some procedures such as capillary blood collection. Non-nutritive suctioning is recommended for isolated painful procedure, such as capillary or venous puncture or intramuscular injection. The onset of suction is recommended 2 minutes before performing the procedure.

SWEETENED SOLUTIONS: Several studies involving term and preterm newborns show that, during capillary and venipuncture blood collection or during circumcision, sweetened solutions decrease crying time, attenuate facial mimetic pain, and reduce the physiological response to pain, compared to distilled water and to the non-nutritional suction itself. Among the several solutions studied, the most effective seems to be water added with sucrose, followed by the glycoside solution. Therefore, it is possible to recommend the clinical use of the glycosylated solution at 25% or 30% for full term (2.0 mL) and for premature infants (0.5 mL), administered in the anterior portion of the tongue about two minutes before small procedures such as capillary or venous puncture. However, one should remember that the use of sweetened solutions only reduces pain scores by 20%. Thus other methods of analgesia should be used together such as, for example, non-nutritional suction or skin-to-skin contact. These solutions can be applied to extremely low birth weight infants who already receive an enteral diet (any volume).

PHARMACOLOGICAL PAIN TREATMENT

NON-OPIOID ANALGESICS

Non-hormonal anti-inflammatories are the main drugs in this group and act by inhibiting prostaglandins and thromboxane, released during tissue aggression. They are indicated in mild or moderate painful processes and/or when pain is associated with an inflammatory process, especially in situations in which respiratory depression triggered by opioids is worrisome and undesirable.

Non-hormonal anti-inflammatories include acetaminophen, acetylsalicylic acid, diclofenac, ibuprofen, indomethacin, naproxen, ketorolac and dipyrone, among others. Except for paracetamol, none of these drugs is available for analgesic use in the neonatal period, not even indomethacin and ibuprofen, which have been widely used for the pharmacological induction of ductus arteriosus closure in preterm infants. Dipyrone should not be used in the neonatal period, as there are no pharmacological and clinical studies regarding this drug in children younger than six years of age.

Paracetamol: is the only drug in this group safe for use in the newborn. It should be administered at the dose of 10-15 mg/kg/dose every 6-8 hours in the full-term patient and 10 mg/kg/dose every 8-12 hours in the preterm, preferably orally. The rectal route should not be used because it leads to erratic drug absorption and, in our country; there are no preparations for parenteral administration of paracetamol. This medication is contraindicated in fasting newborns.

ANALGESIC OPIOIDS

They are the most important weapon for pain treatment of critically ill newborns. Opioids inhibit pain afferent to the spinal cord and, simultaneously, activate the descending cortical pathways inhibiting pain, thus leading to analgesia. In addition to acting on receptors specifically related to analgesia, the interaction of this group of drugs with other opioid receptors triggers, parallel to analgesia, respiratory depression, variable degrees of sedation, ileus, urinary retention, nausea, vomiting, tolerance and physical dependence. In addition to these side effects, recent studies have indicated a worse neurological prognosis (increased frequency of peri- intravenous hemorrhage, periventricular leukomalacia and/or death) in extremely low birth weight preterm infants under mechanical ventilation who received morphine from the first hours of life until about 14 days. Such studies show an association of this poor outcome with the presence of hypotension prior to opioid infusion. Therefore, in preterm newborns with a birth weight of less than 1000g, after a careful evaluation of the presence of pain and the indication of the opioid is defined, it is only necessary to start administration if the patients are normotensive. Non-invasive mean blood pressure is considered equal to or greater than gestational age in weeks. Remember, in patients over 1000 grams one must also ensure hemodynamic stability, before starting the opioid infusion. It is also worth mentioning that the scientific literature indicates that if, on the one hand, the presence of pain can lead to undesirable neurological development consequences in the long term, the use of opioids liberally and in high doses seems to be associated with modifications neurological development in childhood and adolescence. That is, opioids are the main therapeutic weapon in pain management of critically ill newborns, but they should only be used during pain and their doses need to be reduced as soon as the pain is controlled until its withdrawal when not there is more pain. Thus, structured pain assessment in patients undergoing pharmacological analgesia is fundamental for their adequate prescription.

Among the most used opioids in the neonatal period, morphine, fentanyl citrate and tramadol (Chart 3), as well as

Chart 3. Morphine, Fentanyl and Tramadol dosages and side effects.

	Morphine	Fentanyl	Tramadol
Intermittent dose	0.05-0.20 mg/kg/dose every 4 hours, IV slow	0.5-4.0 mcg/kg/dose every 2-4 hours, IV slow	5 mg/kg/day divided every 6 or 8 hours, IV or oral
Continuous dose IV	PTNB: 2-10 mcg/kg/h	PTNB: 0.5-1.0 mcg/kg/h	FTNB or PTNB
	FTNB: 5-20 mcg/kg/h	FTNB: 0,5-2,0 mcg/kg/h	0.10 - 0.25 mg/kg/h
Side effects	Bronchospasm, arterial hypotension, respiratory depression, nausea, vomits, urinary retention, tolerance and withdrawal syndrome	Tolerance, withdrawal syndrome, respiratory depression, chest stiffness, ileus, nausea, vomits, urinary retention, bradycardia	Intestinal obstipation, respiratory depression, tolerance and withdrawal syndrome
Drug weaning if used for:	≤ 3 days: sudden discontinuation		< 5 days: sudden discontinuation
	4-7 days: cut 20% of the initial dose per day		5-7d: cut 20% of the initial dose per day
	8-14 days: cut 10% of the initial dose per day		8 to 14 days: cut 10% of the initial dose per day
	> 14 days: cut 10% of the initial dose every 2-3 days		> 14 days: cut 10% of the initial dose every 2-3 days

methadone, are particularly noteworthy for the treatment of withdrawal syndrome after prolonged use of opioids.

Morphine (Table 3): a potent analgesic and a good sedative. The drug may be administered intermittently at the dose of 0.05-0.20 mg/kg/dose every 4 hours, preferably intravenously. When opting for continuous morphine infusion, the analgesic regimen should be started with the following intravenous doses according to the gestational age of the newborn:

- > 37 weeks: moderate pain 5-10 µg/kg/hour
  Severe pain 10-20 µg/kg/hour
- < 37 weeks: moderate pain 2-5 µg/kg/hour
  Severe pain 5-10 µg/kg/hour

Among morphine's side effects, there is histamine release, which leads to bronchospasm, especially in neonates with chronic lung disease, and suppression of adrenergic tone, which are responsible for hypotension - which is more prevalent in hypovolemic patients. In addition, respiratory depression, ileus, nausea, vomiting and urinary retention are also common to all opioids. Tolerance and withdrawal syndrome may happen depending on the duration of drug use and the strategy used for its suspension. For practical purposes, the following morphine withdrawal scheme is proposed, according to the previous use of the drug:

- < 3 days: abrupt suspension.
- 4 to 7 days: cut 20% of the initial dose daily.
- 8 to 14 days: cut 10% of the initial dose daily.
- > 14 days: cut 10% of the initial dose every 2 to 3 days.

Naloxone is an effective morphine antagonist and may be used at a dose of 0.001 mg/kg, to minimize pruritus, or at a dose of 0.01 mg/kg, to reverse respiratory depression and analgesia. Of note, naloxone is contraindicated in patients who have been receiving morphine for more than 5 days, since it leads to the onset of withdrawal syndrome.

Fentanyl citrate (Table 3): can be used at the dose of 0.5 to 4 µg/kg/dose every 2-4 hours, preferably intravenously. Continuous infusion is the most commonly employed delivery technique due to the stability of the drug's serum therapeutic levels. The drawback of this technique is the rapid onset of tolerance, with increasing doses of the drug being required to obtain the desired analgesic level. Fentanyl citrate triggers few adverse cardiovascular effects, occasionally causing mild bradycardia, and it has, therefore, been the opioid of choice in neonatal units in our country for the management of critically ill neonates. It is worth remembering that rapid injection of high doses of the medicine can lead to muscle stiffness, especially in the rib cage. Other side effects, common to all opioids, may be found, such as respiratory depression, intestinal ileus, nausea, vomiting, and urinary retention. When continuous infusion of fentanyl is chosen, the analgesic regimen should be started with the following intravenous doses according to the gestational age of the newborn:

- > 37 weeks: moderate pain 0.5-1.0 µg/kg/hour. And intense pain 1-2 µg/kg/hour
- <37 weeks: moderate pain 0.5 µg/kg/hour. And intense pain 1 µg/kg/hour

After the administration of the drug for a period of more than 3 days, it is mandatory to withdraw it gradually. For practical purposes, the following scheme of fentanyl cut is proposed, according to the previous time of use of the drug:

- <3 days: abrupt cut.
- 4 to 7 days: cut 20% of the initial dose daily.
- 8 to 14 days: cut 10% of the initial dose daily.
- > 14 days: cut 10% of the initial dose every 2 to 3 days.

Naloxone is also an effective antagonist of fentanyl and may be used at a dose of 0.001 mg/kg to minimize pruritus and nausea or at a dose of 0.01 mg/kg to reverse respiratory depression and analgesia. Facing a chest stiffness, the use of 0.01 mg/kg of naloxone associated with curare is indicated. Naloxone is contraindicated in patients who have been receiving fentanyl for more than 3 days because its administration may trigger withdrawal syndrome.

Tramadol (Table 3): with about 1/10 of the analgesic potency of morphine, tramadol has excellent analgesic properties and, in adults, causes less intestinal constipation and respiratory depression than morphine and fentanyl. However, studies in the neonatal period demonstrate that such advantages of tramadol do not occur in the neonatal period, since the release of adrenergic pathways responsible for the attenuation of these effects in adult is immature in the newborn even at term. Tolerance and physical dependence seem to occur in a manner similar to that of classic opioids when tramadol is given for prolonged periods in the neonatal period. Based on isolated clinical research, the medication has been used at the dose of 5 mg/kg/day, divided into three (8/8 hours) or four (6/6 hours) taken orally or intravenously. The drug can also be administered by continuous infusion at the dose of 0.10-0.25 mg/kg/hour. The gradual withdrawal of tramadol is recommended when its use exceeds 5 to 7 days. It is worth mentioning that the use of tramadol should be exceptional, in specific patients with individually discussed indication.

Methadone: rarely used as an analgesic of first choice in the neonatal period. Its main indication is the treatment of opioid withdrawal syndrome, which may appear in newborns of opioid users, and due to the prolonged use of morphine, fentanyl and/or its analogues in the analgesia of newborns critically ill. In this case, respect the equivalence of medications (0.001mg/kg/day of intravenous fentanyl = 0.1 mg/kg/day of methadone). On initial conversion from fentanyl to methadone, calculate the equivalent dose and prescribe 50% of the calculated dose, divided into one (24/24 hours) or two (12/12 hours) doses taken orally. Decrease the doses of oral methadone (20% of the initial dose every 3 days) until withdrawal. It is worth remembering that by selective action on opioid receptors, the sedative effect of methadone is increased in relation to that of morphine and fentanyl. Thus, careful assessment of the patient's overall condition, especially state of consciousness, reactivity, and sleep, is required when switching from traditional opioids to methadone. Excessive doses of methadone are also associated with respiratory depression and constipation.

LOCAL ANESTHETICS

Currently the topical anesthetics available for use in the neonatal period are the eutectic mixture of lidocaine and prilocaine and the lidocaine solution.

EMLA: the eutectic mixture of prilocaine and lidocaine may produce anesthesia on intact skin, provided that the area of skin covered by the anesthetic does not exceed 100 cm^2. It is a useful analgesic for reducing the pain of circumcision, but it does not relieve the pain of the capillary puncture, probably due to the accelerated whitening of the calcaneus anesthesia, which is highly vascularized. In terms of venous, arterial, lumbar punctures, insertion of central catheters and thoracic drains, among other procedures, data on the efficacy of EMLA® is sparse and do not enable a definitive conclusion. In any case, EMLA® is not routinely used in neonatal intensive care units because it is necessary to wait 60-90 minutes to obtain the anesthetic effect; it causes vasoconstriction, making venipuncture and blood collection difficult; and cannot be used repeatedly for the risk of methemoglobinemia.

Lidocaine: Local infiltration of lidocaine is recommended in neonates submitted to CSF tap, catheter insertion, thoracic drainage and, eventually, arterial puncture. 0.5% lidocaine without epinephrine should be injected at a dose of 5 mg/kg (1 mL/kg). If such concentration is not available in the unit, the drug should be diluted in 0.9% saline. Interestingly, mixing lidocaine with sodium bicarbonate (10 ml of lidocaine and 1 ml of 8.4% sodium bicarbonate) increases the pH of the solution, accelerating the onset of anesthetic action and eliminating pain from injection. The topical anesthetic should be administered subcutaneously after adequate cleaning, with immediate onset of action and effect duration between 30 and 60 minutes after injection. Intravenous injection of lidocaine or the use of excessive doses of the drug may cause lethargy, convulsions, myocardial depression and cardiac dysrhythmias. In view of such clinical manifestations, airway permeability and blood volume should be maintained, in addition to treating convulsions with intravenous sodium phenobarbital.

GENERAL ANESTHETICS

The use of anesthetics is, in general, limited to the intraoperative period of patients with surgical pathologies, and neonatologists have little familiarity with this class of drugs. Among the anesthetics, there are reports of the use of ketamine and propofol. It is important to remember that there are no studies regarding the pharmacokinetics, pharmacodynamics and safety of ketamine and propofol in full term and preterm newborns. Studies in animal models show that the exposure of infants to some anesthetics and sedatives is associated with memory and learning deficits in children and other neurodegenerative changes in the central nervous system. Since ketamine is sometimes used in neonatal intensive care, patients with complex diseases and hospitalized for a very long period, the section below highlights some of the characteristics of this drug.

Ketamine: produces intense analgesia and amnesia. The potential benefits of opioids include the stimulation of the cardiovascular system, the release of catecholamines, and the stimulation of the respiratory center, with bronchodilation and increased pulmonary compliance. The disadvantages of its use in the newborn include arterial hypertension, increased intracranial pressure, increased pulmonary vascular resistance in patients with persistent

pulmonary hypertension and increased amount of bronchial and salivary secretion, as well as the appearance of hallucinations. It is indicated for analgesia during painful procedures in children with congenital heart diseases, obstructive airways diseases, hemodynamic instability and in patients without a venous access. The infusion of ketamine should be accompanied by the administration of midazolam and atropine, according to Chart 4. It is worth remembering once again that the use of ketamine in the neonatal unit is an exception, being restricted to the specific indications outlined above, which should be thoroughly discussed before its use.

To summarize the practical use of pharmacological analgesia in the neonatal period, Chart 5 shows the indications and dosage of pharmacological analgesia for painful procedures or diseases with inflammatory/painful component common in the neonatal ICU.

SEDATION IN THE NEWBORN

Sedatives are pharmacological agents that decrease the patient's activity, anxiety and restlessness, and may lead to amnesia of painful or of non-painful events, but they do not reduce pain. Such medications are used to reduce the level of consciousness and to calm the patient, decrease their spontaneous movement, and induce sleep.

The indication of sedatives is restricted to diagnostic procedures that require some degree of patient immobility, such as computed tomography and magnetic resonance imaging, among others. Aside from this group of indications, the administration of sedatives in the neonatal period should be discouraged, especially in extremely low birth weight infants, and when applied continuously for prolonged periods. This is because sedatives do not promote analgesia and the prognosis of newborns receiving

Chart 4. Ketamine in the neonatal period - dosage, action onset and duration

	EV	IM	VO
Ketamine	0.25-0.5 mg/kg	2-3 mg/kg	4-6 mg/kg
Action onset	0.5-2 minutes	5-15 minutes	20-45 minutes
Duration	20-60 minutes	30-90 minutes	60-120 minutes
Midazolam	0.05 mg/kg	0.05-0.1 mg/kg	0.5 mg/kg
Atropine	0.01 mg/kg	0.01-0.02 mg/kg	0.02-0.03 mg/kg

Chart 5. Pharmacological analgesia for painful procedures or diseases with inflammatory/painful component common in the Neonatal ICU

Procedures or diseases	Analgesia	When to start
Necrotizing enterocolitis with or without perforation	Tramadol: 0,1-0,25 mg/kg/h - IV Fentanyl: 0,5-1,0 µg/kg/h - IV	After the diagnosis
Bone fractures	Tramadol: 5 mg/kg/day every 6h or 8/8h - IV or SOG Paracetamol: 10-15mg/kg 2 to 4 times a day - SOG	After the diagnosis
Percutaneous venous catheter	Tramadol: 1,3 -1,7 mg/kg - IV	15 - 30 minutes before
Phlebotomy	Lidocaine: 0,5 - 1ml/kg (topical) and Tramadol: 1,3 - 1,7 mg/kg - IV or Fentanyl: 1,0 - 2,0 µg/kg - IV slow, in 10 minutes	1 - 2 minutes before 15 - 30 minutes before 10 minutes before
Dialysis catheter insertion	Lidocaine: 0,5 - 1ml/kg (topical) e Tramadol: 1,3 - 1,7 mg/kg - IV or Fentanyl: 1,0 - 2,0 µg/kg - IV slow, in 10 minutes	1 - 2 minutes before 15 - 30 minutes before 10 minutes before
CSF tap	Lidocaine: 0,5 - 1ml/kg (topical)	1 - 2 minutes before
Tracheal intubation	Fentanyl: 1,0 - 2,0 µg/kg - IV or Tramadol: 1,3 - 1,7 mg/kg - IV	10 minutes before 15 - 30 minutes before
Mechanical ventilation	Fentanyl: 0,5 µg/kg/h - IV	After VM onset if there is pain
Chest drainage	Lidocaine: 0,5 - 1ml/kg (topical) e Tramadol: 1,3 - 1,7 mg/kg - IV or Fentanyl: 1,0 - 2,0 µg/kg - IV slow, in 10 minutes	1 - 2 minutes before 15 - 30 minutes before 10 minutes before
Small surgeries (Herniorrhaphy, Postectomy and others)	Tramadol: 5 mg/kg/day every6h or 8/8h - IV or SOG Paracetamol: 10-15mg/kg 2 to 4 times a day - SOG	2 a 4 hours after the surgery
Medium-size surgeries (VPS, GTM, TQT Meningomielocele)	Fentanyl: 0,5 - 1,0 µg/kg/h - IV	2 a 4 hours after the surgery
Large surgeries (Laparotomy, Thoracotomy)	Fentanyl: 0.5 - 1.0 µg/kg/h - IV	4 to 6 hours after the end of the procedure

IV: intravenous; ogt: orogastric tube; VPS: ventriculoperitoneal shunt; GTM: gastrostomy; TQT: tracheostomy.

long-term sedatives is unknown, with indications that their application not only increases the period of mechanical ventilation of patients, but may increase the risk of intra- and periventricular hemorrhage in preterm infants, in addition to potentially interfering in the neurological development of the patient. Thus, in the neonatal ICU, before the prescription of sedatives, all possible causes of agitation should be properly investigated and treated, which includes the pain, hypoxemia, hyperthermia, inflammatory lesions and others.

Among the sedatives available for use in the newborn are barbiturates (short action: thiopental, intermediate action: pentobarbital and prolonged action, phenobarbital), benzodiazepines (diazepam, midazolam and lorazepam) and dexmedetomidine. Barbiturates are of extremely restricted use in neonatal intensive care units and it is worth remembering that chloral hydrate has been withdrawn from circulation and is not available for use. Thus, the following section will address the main benzodiazepines used in the neonatal period and dexmedetomidine.

Benzodiazepines (Chart 6):

Midazolam may be used intermittently for diagnostic procedures at a dose of 0.05-0.15 mg/kg/dose, slowly in 2-5 minutes, every 2 to 4 hours, or the medication can be instilled intranasally at the dose of 0.2-0.3 mg/kg of the same intravenous preparation. The intravenous drug is compatible with solutions of glucose, saline, distilled water or parenteral nutrition. The onset of action occurs in 5 to 10 minutes and the duration of the sedative effect is 1 to 2 hours. For continuous sedation, available data is insufficient to encourage the use of intravenous injection of midazolam as a sedative for neonates in intensive care, and there are concerns about their safety, with reports of an increase in adverse neurological events at 28 days of age. While lorazepam, although studies in pediatric patients indicate that its interaction with opioids leads to a lower incidence of side-effects, it is not available in our country in its intravenous presentation, limiting its use to patients receiving an enteral diet, prolonged withdrawal scheme of opioids and midazolam or in chronic patients with specific indications for sedation.

Benzodiazepines administration may lead to acute and chronic toxicity. Acutely, they can occur from minor changes, such as paradoxical excitement, to serious problems such as respiratory depression, hypotension and coma. In view of these effects, there is an indication of discontinuing the use of benzodiazepine, maintaining airway permeability, initiating ventilation, monitoring cardiocirculatory conditions and administering the benzodiazepine antagonist. Flumazenil is a pure benzodiazepine antagonist, commercially available as a 10 mL, 0.1 mg/mL injectable solution. The starting dose of the drug is 0.01 mg/kg and may be repeated every 2 minutes up to the total dose of 1 mg (10 mL). In general, there is reversal of unwanted effects in 1-3 minutes and the duration of flumazenil's effect is 45-60 minutes. As the duration of the antagonist's effect is lower than that of the benzodiazepine, the patient should always be monitored for at least 2 hours. Remember that the use of the antagonist may trigger seizures in newborns receiving benzodiazepines to control seizures.

Dexmedetomidine (Precedex®): is a potent selective β2 adrenergic lipophilic agonist agent that provides sedative, anxiolytic, sympatholytic and analgesic effects.

Chart 6. Midazolam and Lorazepam Posology and Side Effects

	Midazolam	Lorazepam
Intermittent dose	Intravenously: 0.05-0.15 mg/kg/dose every 2-4 hours, IV slow, in 2-5 minutes Action onset: 1-3 minutes. Duration: 1-2 hours Intranasally: 0.2-0.3 mg/kg/dose Action onset: 5-10 minutes. Duration: 1-2 hours	Intravenously (not available in Brazil): 0.03-0.05 mg/kg/dose up to 0.1mg/kg/dose every 4-8 hours, IV slow, in 2-5 minutes Per os/gastric tube: 0.05 mg/kg/dose up to every 4-8 hours
IV continuous dose	0,1-0,6 mcg/kg/h Onset of action: 1-3 minutes	----
Side effects	Respiratory depression, arterial hypotension, seizures with fast injections of high doses. Withdrawal syndrome. Care should be taken when combining fentanyl + midazolam: dystonic postures and choreoathetosis (encephalopathy)	Respiratory depression, upper airway obstruction, arterial hypotension
Drug discontinuation regime	Use ≤ 3 days: sudden discontinuation use 4-7 days: cut 20% of the initial dose per day use 8-14 day: cut 10% of the initial dose per day use >14 days: cut 10% of the initial dose every 2-3 days	

BI: bilirrubina indireta; BD: bilirrubina direta; SNC: sistema nervoso central.

The drug acts selectively at α2 post-synaptic receptors (action α2: α1 = 1600: 1), activating the G-proteins and increasing the conductance in the K+ channels, with inhibition of norepinephrine release in the locus coeruleus and in the posterior horn of the spinal cord. It requires hepatic metabolism and its metabolites are eliminated in the urine. Although dexmedetomidine can be administered as a sedative or analgesic in an isolated manner, its larger use should be indicated in combination with other analgesics/sedatives, due to its action sparing additional doses of opioids and benzodiazepines.

When it is administered, the main side effects are bradycardia and hypotension. Studies in older children and infants suggest that the drug has an interesting profile for the postoperative of newborns, as it inhibits the endocrine-metabolic stress response, it has cardio protective properties, besides facilitating extubating, and there are indications of neuroprotective activity.

Studies in the neonatal period are sparse, mainly dealing with series of cases that include a range of patients of diverse ages and clinical conditions. These case series show a short-term safety profile, although bradycardia and systemic hypotension are generally reported without the need for therapeutic intervention, and there is a reduction in the need to stagger doses of opioids and benzodiazepines in concomitant use. Retrospective studies of neonates with heart disease indicate hemodynamic safety of the agent. There is no evaluation of dexmedetomidine in the medium and long term

If a decision is made for the use of the medication, injection should be continuous with no attack dose, starting at 0.2 mcg/kg/hour, and the dose may be escalated to 0.7-1.0 mcg/kg/hour. Studies in adults and older children indicate that it may be administered intravenously, intramuscularly, subcutaneously, nasally, buccally, rectally and orally, but only the intravenous route has been studied in the neonatal period. If used for 72 hours or more, discontinue slowly avoiding withdrawal syndrome.

It is worth mentioning that it is an expensive and little studied medication in the neonatal period, and its safety profile is extrapolated from small series of cases, which brings to the fore the recommendation of a careful and parsimonious indication of this sedative and its preferential use only for the post cardiac surgery in the neonatal period.

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