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PAIN AND STRESS IN THE NEONATE

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SUMMARY

DUREREA ŞI STRESUL ÎN RÂNDUL NOU-NĂSCUȚILOR

Asociația Internațională pentru Studiul Durerii a definit în 1979 conceptul de durere ca „un răspuns senzorial şi emoțional neplăcut asociat cu vătămările prezente sau potențiale ale țesuturilor, sau descrise în termen de astfel de vătămări”.

Sugarii şi fetuşii au capacitatea de a percepe durerea. Substraturile neuroanatomic, neurofiziologic şi neurochimic pentru perceperea durerii se dezvoltă începând de la mijlocul perioadei de gestație şi continuă să se dezvolte în perioada tardivă de gestație şi în copilărie.

Reacțiile la durere a sugarilor născuți în termen şi prematuri sunt atât fiziologice cât şi comportamentale. Expunerea la dureri prelungite sau severe poate creşte cazurile morbidității neonatale prin distrugerea celulelor neuronale. Are loc stimularea celulelor neuronale mediată de receptorul N-metil-D-aspartat (NMDA), cu aflux de calciu. Are loc apoptoza neuronală consolidată, potențial din cauza separării materne sau a factorilor de stres metabolic.

Controlul adecvat al durerii poate atenua unele dintre aceste efecte.

Anand şi Hickey4 descriu schimbările de comportament asociate cu durerea şi le-au împărțit în patru categorii generale: reacție motorie simplă, expresii faciale, plânsul şi reacțiile complexe de comportament. Severitatea durerii şi a efectelor analgezicilor poate fi evaluată la nou-născuți cu ajutorul mijloacelor confirmate. Disponibil în unitatea de terapie intensivă este Profilul durerii la nou-născutul prematur (PIPP), iar în sectiile de îngrijire neonatală: Scorul durerii comportamentale (BPS) sau Nivelul de durere la nou-născuți şi sugari (NIPS) pentru a evalua durerea pre- şi post-intervențională.

Între anii 1985-1992 KJS Anand şi Asociații a publicat literatură radicală care a relevat siguranța relativă a agenților de anestezie şi rezultatele bune la copii şi adolescenți supuşi unei intervenții chirurgicale cu anestezie. După aceste publicații seminale, cercetările în domeniul durerii la nou-născuți, atât clinice, cât şi cele ştiințifice de bază, s-au extins.

Recomandările curente ale Academiei Americane de Pediatrie (AAP)

Comitetul asupra fătului şi nou-născutului (COFN) a extins ghidul pentru evaluarea şi gestionarea durerii şi stresului la nou-născuți. Evaluarea ar trebui să urmeze următoarele:

Îngrijitorii trebui instruiți pentru a evalua durerea la nou-născuți prin utilizarea de instrumente multidimensionale

Nou-născuții trebuie evaluați în mod curent până/după proceduri

Folosirea gradației durerii ajută la ghidarea îngrijitorilor în asigurarea unei alienări eficace a durerii

Principiul trebuie să minimizeze cât mai mult posibil numărul de subminări dureroase în îngrijire

Să utilizeze anestezice topice pentru venipuncție, puncție lombară şi picurătoare

Nu se recomandă utilizarea de rutină a picăturilor de morfină, fentanilă sau midazolam la pacienții cronici ventilați

Să folosească zaharoza/glucoza orală şi alte metode non-farmacologice de reducere a durerii: aspirația non-nutritivă, îngrijirea stil cangur, întinderea facilitată, înfăşarea şi îngrijirea de dezvoltare

Există publicate câteva studii clinice randomizate controlate privind gestionarea durerii la nou-născuți. Studiul NEOPAIN a evaluat analgezia cu perfuzie de morfină de până la 14 zile la sugarii prematuri ventilați. Dozele de morfină folosite în acest studiu au scăzut semnele clinice de durere, dar au fost asociate cu efecte adverse semnificative la sugari prematuri ventilați. Astfel, studiul ar sugera ca morfina să fie utilizată numai la sugarii normotensivi.

Pentru procedurile minim-invazive: Soluție de zaharoză 24% (0,5-1,5 ml)

Proceduri invazive: Narcotice, inclusiv morfina, fentanila şi sedative

Intubația: Fentanilă (1 mcg/kg pînă la 3 mcg/kg), pentru o procedură; În cazul în care sugarul rămîne intubat şi este nevoie de analgezie, se va folosi o perfuzie continuă de fentanilă sau morfină.

Durerea preoperatorie: 1) Sugarii se vor premedica cu fentanilă cu o oră înainte de transferul în sala chirurgicală în cazul în care sunt intubați; altfel, aceasta se va administra la SAU înainte de intubație; 2) Pentru revenire – dacă este necesar, se fa folosi nalaxon (Narcan 0,1 mg/kg) pentru tratarea sugarilor cu efecte adverse excesive în urma administrării de opoide; poate fi titrat pentru a păstra careva efecte analgezice.

Резюме

БОЛЬ И СТРЕСС У НОВОРОЖДЕННЫХ

В 1979 г. Международная Ассоциация по изучению боли предложила следующее научное определение: «Боль — это неприятное ощущение и эмоциональное переживание, связанное с текущим или потенциальным тканевым повреждением или описываемое в терминах такого повреждения».

Плод и новорожденные обладают способностью воспринимать боль. Нейроанатомические, нейрофизиологические и нейрохимические структуры, отвечающие за восприятие боли, развиваются, начиная с середины беременности, продолжая развиваться на поздних сроках беременности и в детстве.

Реакция на боль у доношенных и недоношенных детей носят физиологический и поведенческий характер. Длительное воздействие боли, а так же сильной боли, может увеличить случаи заболеваемости новорожденных посредством разрушения нервных клеток. Стимуляция нервных клеток происходит за счет рецептор-опосредованного N-метил-D-аспартата (NMDA), а так же за счет притока кальция. Имеет место обширный апоптоз нейронов, вероятно возникающий в связи с отлучением от мамы или метаболическим стрессом.

Адекватный контроль боли может облегчить некоторые из этих эффектов.

Ананд и Хики4 описывают поведенческие изменения, связанные с болью, которые были подразделены ими на четыре основные категории: простая двигательная реакция, мимика, плач и сложные поведенческие реакции. Тяжесть боли и обезболивающего эффекта у детей могут быть оценены с помощью подтвержденных инструментов. В Отделении Интенсивной Терапии в наличии имеется Профиль боли у недоношенных новорожденных (PIPP), а в Отделениях по уходу за новорожденными: Оценка поведенческой боли (BPS), или Уровень боли у новорожденных и грудных детей (NIPS) для оценки боли до и после вмешательств.

Существует несколько опубликованных рандомизированных контролируемых исследований о лечении боли у новорожденных. Исследование NEOPAIN оценивало болеутоляющий эффект инфузий морфина в течение 14 дней у вентилируемых недоношенных новорожденных. Дозы морфина, используемых в данном исследовании, снизили клинические признаки боли, но привели к значительным побочным эффектам у вентилируемых недоношенных детей. Таким образом, исследование показало, что морфин следует использовать только у младенцев с нормальным артериальным давлением.

Despite the fact that the field of neonatology has dramatically reduced infant morbidity and mortality over the past several decades, under-treatment of pain and stress continues. It is estimated that some infants in the neonatal intensive care unit (NICU) experience over 7000 painful procedures before discharge. Humanitarian and scientific principles favor improved management of strategies to prevent pain and stress in the neonate.

The American Academy of Pediatrics (AAP) has published recommendations for the assessment and appropriate treatment of pain. Also, the clinician has many tools for this assessment including an updated N-PASS tool for appropriate evaluation of pain and stress in the neonate. Short-term and long-term sequelae of acute and chronic pain are now validated.

Instruction

The field of neonatology, established in the past several decades, has dramatically reduced infant morbidity and mortality. The performance of frequent and more invasive procedures has been an integral part ofthis advancement. It is now recognized that both premature and full-term infants experience pain and stress related to these procedures.

Until the 1980s, newborns underwent invasive procedures, including surgery, without administration of analgesic or anesthetic agents administered. The reasons for the lack oftreatment were multifaceted and included the following:

- Immature neonatal brain could not respond in a manner that perceived or localized painful stimuli
- Clinicians assumed that neonates did not experience pain as severely as adults and could not rememberthe pain
- Misconception stems from the lack of ability to communicate verbally
- Concerns about the potential adverse side effects of analgesic or anesthetic agents overwhelmed the perceived benefit

What Is Pain?

The International Association for the Study of Pain defined pain in 1979 as "an unpleasant sensory and emotional response associated with actual or potential tissue damage, or described in terms of such damage." Pain is always subjective. This is clearly problematic when considering the preverbal nature of the fetus, neonate, and infant. The inability to communicate verbally has led to this misconception.

Pain perception is dependent on two components. One is a sensory component that is neurophysiologically determined and the other is an emotional component based on affective factors, past experience, and development.

Pain may be described as a process in which the stimulation of peripheral sensory nociceptors produces responses conducted via the spinal cord neurons to sensory areas of the cerebral cortex (Table 1).

Evidence suggests that the density of cutaneous nociceptors in the late fetus and neonate is comparable to or greater than those found in adults.

When did the reality of pain change?

Between 1985-1992, KJS Anand and Associates1-3 published radical literature that revealed the relative safety of anesthetic agents and improved outcomes of pediatric patients undergoing surgery with anesthesia. After these seminal publications, neonatal pain research, both clinical and basic science, blossomed. Awareness by neonatal practitioners was increased. Presently, assessment and control of pain is part of the Joint Commission's hospital evaluations and must be in place for the hospital to receive accreditation.

Principles of the development of pain perception

It is now recognized that neuroanatomical, neurophysiologic, and neuroendocrine systems of the neonate are sufficiently developed to allow transmission of painful stimuli.

Catecholamine, corticosteroids, growth hormone, and glucagon are developed in the fetus and newborn. During painful stimuli, there is a difference in cerebral blood flow (CBF) with males having increased CBF to both sides of the brain, resulting in them requiring more narcotics and sedatives than females.

A review of the literature indicates that infants, including preterm infants, experience both immediate and long-lasting harmful consequences of structural and physiologic changes associated with exposure to severe or repetitive pain. Exposure to prolonged or severe pain may increase neonatal morbidity by causing neuronal cell death. N-methyl-D- aspartate (NMDA) receptor-mediated neuronal cell stimulation occurs with calcium influx initiating excitotoxic cell death. Enhanced neuronal apoptosis, potentially due to maternal separation or metabolic stressors, occurs. Neonates who have experienced pain during the neonatal period respond differently to subsequent painful events such as immunizations.

Behavioral And Physiologic Response To Pain

Peripheral sensory nociceptors produce responses conducted via the spinal cord neurons to sensory areas of the cerebral cortex. Nerve terminals exist on all body surfaces by 22-29 weeks of gestation and the fetus is capable of sensing painful stimuli. Overlapping terminals create local hyper- excitable networks, which enable even low- threshold stimuli to produce an exaggerated pain response. Physiologic responses include an increase in catecholamine resulting in an increase in HR, BP, and intracranial pressure. These changes occur as early as 23 weeks of gestational age.

Assessment Of Pain

Anand and Hickey4 describe the behavioral changes associated with pain and divided them into four general categories: simple motor response, facial expressions, crying, and complex behavioral responses. Severity of pain and effects of analgesia can be assessed in the neonate using validated instruments. Newborns are usually not easily comforted when analgesia is needed. The clinician should be aware that a lack of behavioral responses (ie, crying and movement) does not necessarily indicate the absence of pain.

Table 1

Development of cutaneous sensory receptors occurs as follows:

Weeks of Gestation	Location of Receptors
7th Week	Perioral region
11th Week	Face, palm, and soles
15th Week	Trunk, arms, and legs
20th Week	All cutaneous and mucous surfaces

There are a number of validated and reliable scales of pain assessment. Available in the NICU is (1) premature infant pain profile (PIPP), which is based on the facial expression of the infants, along with physiologic measures in the context of gestational age and alertness. Available in the intermediate care or well-baby nurseries are the (2) behavioral pain score (BPS) or the (3) neonatal infant pain scale (NIPS), which is a tool that can be used to assess pre- and post-interventional pain.

Another scale for the assessment of pain in the NICU, which includes changes in vital signs, is the NPASS (Neonatal Pain, Agitation, and Sedation Scale).5 The scale's reliability and validity was published in 2008 and 2010 for use in prolonged or acute pain. Table 2 contains the most current version shared by the author.

Use Of The NIPS And N-PASS In A Case Scenario In The NICU

This 28 6/7 weeks gestation age female was admitted to the NICU at Kosair Children's

Hospital with diagnoses of prematurity, rule- out sepsis, and respiratory distress syndrome. The baby was intubated and had a nasogastric tube in place when N-PASS scoring began at 24 hours of age. Prior to the N-PASS scoring, the NIPS score was 0. The baby scored a 1 on the Pain Scale of the N-PASS and a 5 score on the Sedation Scale even though the infant had not received medications for sedation.

Ifthe blood culture had been positive, this could have been a contributing factor to the decreased reaction to stimuli which was seen in this patient. According to Hummel, 6 a sedation score when sedation medication has not been given could be a potential sign of prolonged pain or stress to the infant. During this same time frame the pain score from the NIPS

Table 1

Neonatal Pain, Agitation, and Sedation Scale

Assessment Criteria	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 crying at intervals Consolable	High-pitched or silent-continuous cry Inconsolable
Behavior State	No arousal to any stimuli No spontaneous movement	Arouses minimally to stimuli Little spontaneous movement	No sedation/ No pain signs	Restless, squirming Awakens frequently	Arching, kicking Constantly awake or Arouses minimally / no movement (not sedated)
Facial Expression	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 ↓ muscle tone	No sedation/ No 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 SaO_2 76-85% with stimulation - quick ↑	↑ > 20% from baseline SaO_2 < 75% with stimulation - slow t Out of sync/fighting vent

scale was 0. Therefore, this is a scenario where a premature infant may have been exhibiting signs of pain through decreased movement from stimulation. The prolonged stress could potentially have been related to overstimulation and/or intubation.

Three days later, the same baby was again scored using the N-PASS and NIPS. The baby had been extubated to 5 cms of Bubble CPAP (continuous positive airway pressure) and had an orogastric tube. The N-PASS scores were between 2 and 4 while the NIPS was 0. The baby did not exhibit signs for a sedation score to be used at this time.

The score of 4 was treated with a repositioning and decreasing stimulation in the environment, which decreased the N-PASS score to 2. According to Hummel (2009), a score of 3 or below is the goal after an intervention. The only signs of pain that were exhibited were clenched toes, fists, orfinger splay and 1 point was added for prematurity.

Current Americian Academy Of Pediatrics (AAP) Recommentations

The Committee on the Fetus and Newborn (COFN) expanded guidelines for assessment and management of pain and stress in the newborn. The assessment should follow the following guidelines:

- The caregivers should be trained to assess neonates for pain using multidimensional tools

Assessment of Sedation

- Sedationis scored in addition to pain for each behavioral and physiological criteria to assess the infant's response to stimuli
- Sedation does not need to be assessed/scored with every pain assessment/score
- Sedationis scored from 0→-2 for each behavioral and physiological criteria, then summed and noted as a negative score (0 → -10)
  - A score of 0 is given if the infant has no signs of sedation, does not under-react
- Desired levels of sedation vary according to the situation
  - "Deep sedation" → goal score of -10 to -5
  - "Light sedation" → goal score of -5 to -2
  - Deep sedation is not recommended unless aninfant is receiving ventilatory support, related to the high potential for hypoventilation and apnea
- A negative score without the administration of opioids/ sedatives may indicate:
  - The premature infant's response to prolonged or persistent pain/stress
  - Neurologic depression, sepsis, or other pathology

Paralysis/Neuromuscular blockade

- It is impossible to behaviorally evaluate a paralyzedinfant for pain
- Increases in heart rate and blood pressure at rest or with stimulation may be the only indicator of a need for more analgesia
- Analgesics should be administered continuously by drip or around-the-clock dosing
  - Higher, more frequent doses may be required if the infant is post-op, has a chest

tube, or other pathology (such as NEC) that would normally cause pain
- Opioid doses should be increased by 10% every 3-5 days as tolerance will occur without symptoms of inadequate analgesia

Premature Pain **Assessment**

+ 1 if <30 weeks gestation / corrected age

Assessment of Pain/Agitation

- Pain assessment is the fifth vital sign - assessment for pain should beincluded in every vital sign assessment
- Pain is scored from 0→+2 for each behavioral and physiological criteria, then summed
  - Points are added to the prematureinfant's pain score based on the gestational age to compensate for the limited ability to behaviorally communicate pain
  - Total pain scoreis documented as a positive number (0 → +11)
- Treatment/interventions are suggested for scores > 3
  - Interventions for known pain/painful stimuli are indicated before the score reaches 3
- The goal of pain treatment/intervention is a score < 3
- More frequent pain assessment indications
  - Indwelling tubes or lines which may cause pain, especially with movement (e.g. chest tubes) → at least every 2-4 hours
  - Receiving analgesics and/or sedatives → at least every 2-4 hours
  - 30-60 minutes after an analgesic is given for pain behaviors to assess response to medication
  - Post-operative → at least every 2 hours for 24-48 hours, then every 4 hours until off medications

Scoring Criteria

Crying / Irritability

-2 → No response to painful stimuli

* No cry with needle sticks
* No reaction to ETT or nares suctioning
* No response to care giving

-1 → Moans, sighs, or cries (audible or silent) minimally to painful stimuli, e.g. needle sticks, ETT or nares suctioning, care giving

O → No sedation signs or No pain/agitation signs

+ 1 → Infant is irritable/crying at intervals - but can be consoled

* If intubated - intermittent silent cry

+2 → Any of the following

* Cry is high-pitched
* Infant cries inconsolably
* If intubated - silent continuous cry

Behavior / State

-2 → Does not arouse or react to any stimuli:

* Eyes continually shut or open
* No spontaneous movement

-1 → Little spontaneous movement, arouses briefly and/or minimally to any stimuli

* Opens eyes briefly
* Reacts to suctioning
* Withdraws to pain

O → No sedation signs or No pain/agitation signs

+ 1 → Any of the following

* Restless, squirming
* Awakens frequently/easily with minimal or no stimuli

+2 → Any of the following

* Kicking
* Arching
* Constantly awake
* No movement or minimal arousal with stimulation (not sedated, inappropriate for gestational age or clinical situation)

Extremities / Tone

-2 → Any of the following

* No palmar or planter grasp can be elicited
* Flaccid tone

-1 → Any of the following

* Weak palmar or planter grasp can be elicited
* Decreased tone

O → No sedation signs or No pain/agitation signs

+ 1 → Intermittent (<30 seconds duration) observation of toes and/or hands as clenched or fingers splayed

* Body is nottense

+2 → Any of the following

* Frequent (>30 seconds duration) observation of toes and/or hands as clenched, or fingers splayed
* Body is tense/stiff

Vital Signs: HR, BP, RR, & O2 Saturations

-2 → Any of the following

* No variability in vital signs with stimuli
* Hypoventilation
* Apnea
* Ventilated infant - no spontaneous respiratory effort

-1 → Vital signs show little variability with stimuli - less than l0% from baseline

O → No sedation signs or No pain/agitation signs

+ 1 → Any of the following

* HR, RR, and/or BP are 10-20% above baseline
* With care/stimuli infant desaturates minimally to moderately (SaO2 76-85%) and recovers quickly (within 2 minutes)

+2 → Any of the following

* HR, RR, and/or BP are > 20% above baseline
* With care/stimuli infant desaturates severely (SaO2 < 75%) and recovers slowly (> 2 minutes)
* Out of sync/fighting ventilator

Facial Expression

-2 → Any of the following

* Mouth is lax

* Drooling
* No facial expression at rest or with stimuli

-1 → Minimal facial expression with stimuli

O → No sedation signs or No pain/agitation signs

+ 1 → Any pain face expression observed intermittently

+2 → Any pain face expression is continual

• Neonates should be routinely assessed before/after procedures

• Use of pain scale helps to guide caregivers in the provision of effective pain relief

• Principle should be minimizing the number of painful disruptions in care as much as possible

• Use topical anesthetics for venipuncture, lumbar puncture, and IV placement

• Routine use of drips of morphine, fentanyl, or midazolam in chronically ventilated patients is not recommended

• Use oral sucrose/glucose and other non-pharmacologic pain reduction methods: nonnutritive sucking, kangaroo care, facilitated tuck, swaddling, and developmental care

Major Surgery

• All hospitals should have established protocols for pain management including perioperative period

• Sufficient anesthesia should be provided to prevent intra-operative pain and stress to decrease post-op analgesic requirements

• Use of a pain scale post-op

• Opioids should be used (regional anesthesia)

• Consider acetaminophen if >28 weeks

• Chest tube placement and removal

• Local anesthetic used for skin infiltration

• Retinal surgery

• Peripheral central line placement

• Peripheral arterial line placement

• Retinal examination (questionable)

Treatment Of Pain

There are few published randomized controlled trials (RCTs) of pain management in the neonate. One such trial was the NEOPAIN trial which evaluated analgesia with morphine infusion up to 14 days in ventilated preterm infants. Overall, pre-emptive morphine infusions did not reduce the primary composite of neonatal death, severe intraventricular hemorrhage (IVH), or periventricular leuko- malacia (PVL) in ventilated preterm infants. The post-hoc analysis did show an increase in severe IVH in the subgroup of 27-29 weeks GA, and an increased rate in the composite in those who received intermittent boluses of open-label morphine. It appears that the

adverse outcomes were in those infants who were hypotensive before the drug infusion was initiated.

The morphine doses used in this study decreased clinical signs of pain but were associated with significant adverse effects in ventilated preterm infants.

Facial expression of physical distress and pain in the infant

Therefore, this study would suggest that morphine be used only in infants who are normotensive.7

For minimally-invasive procedures:

• Sucrose 24% solution (0.5 -1.5 ml)

Invasive procedures:

• Narcotics including morphine, fentanyl and sedatives

Intubation:

• Fentanyl (1 mcg/kg to 3 mcg/kg) for the procedure

• Ifthe infant remains intubated and analgesia is needed, then use a continuous infusion offentanyl or morphine

Preoperative pain:

• Premedicate infants with fentanyl one hour before transferring to the surgical suite if intubated; otherwise, give in the ORjust before intubation

• Reversal—if required, naloxone (Narcan 0.1 mg/kg) is used to treat infants who have excessive side effects of opoids; may be titrated to keep some ofthe analgesic effect

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