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PAIN IN NEONATES

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ABSTRACT

A study in the purpose of pain assessment in neonates and relief of pain cycles; not only for ethical view but also because repeated painful exposures can cause deleterious consequences. Gathered information from various medical references and previous studies discussing pain physiology, modulation and pain calibration instruments all are provided for this purpose. In Egypt, pain in neonates is underestimated and it's prevalent among the public that circumcision is preferably carried out in the first week. And from this point, we were determined to make this study about pain in neonatal age.

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INTRODUCTION

Physiology of pain in neonates

The "standard" definition of pain is that of the International Association for the Study of Pain which states that it is an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage, always subjective (Argoff, 2009).

Modulation of pain

Modulation of pain occurs peripherally at the nociceptor, in the spinal cord, or in supraspinal structures (central). This modulation can either inhibit (suppress) or facilitate (aggravate) pain (Apkarian *et al*., 2005).

A.Peripheral modulation:

•Primary hyperalgesia:

Sensitization of the nociceptors results in a decrease in pain threeshold, an increase in the response to the same stimulus intensity, a decrease in response latency and spontaneous firing even after cessation of the stimulus. Primary hyperalgesia is mediated by the release of alogens from damaged tissues. Bradykinin is released from tissues following activation of factor XII. Bradykinin activates free nerve endings via specific receptors (B1 and B2) (Wiech and Ploner, 2008).

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•Secondary hyperalgesia:

It is manifested by the "triple response" of a red flush around the site of injury (flare), local tissue edema, and sensitization to noxious stimuli. Secondary hyperalgesia is primarily due to antidromic release of sP (and probably CGRP) from collateral axons of the primary afferent neuron.

B.Central modulation

a.Facilitation:

At least three mechanisms are responsible for central sensitization in the spinal cord:

1- Wind-up and sensitization of second-order neurons. WDR neurons increase their discharge frequency with the same repetitive stimuli, and exhibit prolonged discharge, even after afferent C fiber input has stopped.
2- Receptor field expansion. Dorsal horn neurons increase their receptive fields such that adjacent neurons become responsive to stimuli (whether noxious or not) to which they were previously unresponsive.
3- Hyperexcitability of flexion reflexes. Enhancement of flexion reflexes is observed both ipsilaterally and contra laterally.

b.Inhibition:

Transmission of nociceptive input in the spinal cord can be inhibited by segmental activity in the cord itself, as well as descending neural activity from supraspinal centers.

Etiology of acute pain in neonates

A.Invasive procedures in NICU

Preterm and term neonates admitted to the NICU are exposed to numerous and varied sources of pain and stress some for investigation and some for treatment (Porter and Anand, 1998). In children and adults, pain produced by such procedures is recognized and treated on humanitarian grounds. In the sick infant invasive procedures can cause major physiological disturbances, which can be reduced by providing analgesia (Speidle, 1998).

Table 1. Painful procedures performed in neonatal intensive care units

Diagnostic	Therapeutic	Surgical
-Arterial puncture -Heel lancing -Lumbar puncture. -Retinopathy of prematurity examination -Suprapubic bladder tip -veni puncture -eye examination	-Bladder catheriziation. -central line insertion/ removal -Chest tube insertion/ removal -Chest physiotherapy -Dressing change -Gavage tube insertion -Intra muscular injection -Postural drainage -removal of adhesive Tap -ventricular Tap -Tracheal intubation/extubation -Suture removal	-Other surgical Procedures -Peritoneal Drain -Venous Cut down

(Anand, 2001)

B.Birth events

Although they are rare occurrence, scalp lacerations, sever head molding and clavicular fractures are sources of new born pain (Van Lingen *et al*., 2001).

C.Environmental causes of pain

- Noise pollution:

Safety standards require that the mean noise levels inside an incubator should not exceed 60 decibels (Long *et al*., 2000).

- Ambient light exposure:

Light may damage the retinas of extremely low birth weight babies (Glass *et al*., 1995).

- Handling.
- Daily rhythms and deep sleep:

In most intensive care units there is no clear pronounced diurnal rhythm in noise and light intensity and staff activities (Lawson *et al*., 1997).

Determinants of premature infants to pain

- Gestational age
- Prior exposure to painful procedure
- State and response to pain
- Severity of illness
- Gender

Impact of pain on neonates

A.Immediate response of the neonate to painful stimuli
B.Long-term effects of neonatal pain

A.Immediate response of the neonate to painful stimuli

Immediate response to pain can be protective, the response allows the individuals to mobilize energy and resources to the site of injury and activate autonomic nervous system to serve as warning signal for potentially damaging stimuli. (Mitchell and Boss. 2002).

a.Behavioral

1-Facial expression

This is the most comprehensively studied behavioral response; as it is considered the most reliable indicator of pain across population and type and, as such, should be considered the gold standard of behavioral response of pain in infants. The facial expressions of infants experiencing acute pain include: nasal roots broadened and bulged, depended nasolabil furrow, a square mouth and a taut cupped tongue. (Grunau and Craig, 1987).

The behavioral state of infants immediately before painful stimulation affects the robustness of the response. Infants in a deep sleep state shows less vigorous facial expressions (Stevens *et al*., 1994). An interesting finding is that female neonates of all gestational ages expressed more facial features of pain than male infant during capillary puncture (McIntosh *et al*., 1993).

2-Crying

The pain cry has specific behavioral characteristics and spectrographic properties in healthy full term neonate (Anand *et al*., 1988). In a series of studies by (Fuller 1995); (Fuller and Horii 1996) and (Horii, 1998), they found that the acoustic characteristics of infants cries differs between hunger, pain and cooing cries, the main scores for the cry pitch measured in HZ was higher in hunger and pain further in cooing , pitch was significantly higher for hunger than for pain cries.

3-Body movement

In a study by **(Holsti *et al*., 2007)**, the frequency of behaviors as judged by "New Born Individualized Development Care and Assessment Program" (NIDCAP) were investigated in relation to pain or clustered care in preterm infants and the following results were noted.

Table 2. Body movements in pain and during clustered care

Body movements	In pain	During clustered care
Flex arms	8.1	9.1
Flex legs	5.5	5.6
Extended legs	8.6	16.9
Hand on face	3.8	11.9
Finger splay	5.1	40.3
Statue	3.5	13.5
Frown	11.4	8.2
Yawning	3.4	36.9
Tongue extension	0.9	14.4
Extended arms	1.1	31.6
Airplane	0.4	6.1
Sit on air	3.2	6.0
Hand to mouth	1.2	4.7
Fisting	1.6	6.1

b. Physiological

1-Vital signs

i. Heart rate: Too many studies proved that neonatal pain increases in heart rate by up to 11%. Interestingly, they showed also that the relation between pain and heart rate response was gender related i.e. it was only found in male subjects (Tousignant *et al.,* 2005).
ii. Blood pressure:(Gessler *et al*., 2004) showed that blood pressure increased after painful stimulation which was confirmed later by Taksande (2005).
iii. Respiratory rate: Respiratory rate was found to increase significantly in response to painful procedures (Tousignant *et al*., 2005).

2-Oxygen saturation: Significant decrease in oxygen saturation occurs in response to painful stimuli, this was reported by (Anand *et al*. 1988) and (Harmesh *et al*. 2000).

3-Autonomic changes: Pain can cause several autonomic changes in the neonate such as mydriasis, sweating flushing and pallor (Mathew *et al*., 2003).

4-GIT: Pain can cause gastric stasis, gastric dilation or ileus (Golianu *et al*., 2000).

5-Hormonal changes: Cortisol, catecholamine, glucagon, growth hormone, rennin, aldosterone and ADH all increase by pain, while insulin decreases (Mathew *et al*., 2003).

6-Metabolic changes: The above hormonal responses lead to the following metabolic changes hyper metabolism, hyperglycemia, protein catabolism and lipolysis (Golianu *et al*., 2000).

7-Haemotalogical and immune reactions: Platelet aggregation, hypercoagulability, venous stasis, increased fibrinolysin, altered immune function and cytokine production are consequences of neonatal pain (Golianu *et al*., 2000).

8-CNS alteration: It was found that multiple invasive procedures in premature infants cause marked fluctuations in intracranial pressure leading to early Intraventricular Hemorrhage (IVH) or periventricular leukomalacia.

B.Long-term effects of neonatal pain

a.Effect on pain sensitivity later in life

1-In term infants

In one of the most cited studies, term born males who had undergone unanaesthesized neonatal circumcision, responded more intensely to mmunization at age 4-6 months than uncircumcised infants, pretreatment with EMLA cream partially attenuated this hypersensitivity (Taddio *et al*., 1997). However, it was found that hypersensitivity is not restricted to the ipsilateral side of tissue damage but extends to the contralateral side. (Andrews and Fitzgerald, 2002)

2-In preterm neonates

•**Heightened response:** It is well established that preterm infants have heightened tactile sensitivity **(Fitzgerld, 2005)** and react behaviorally and physiologically to invasive procedures later in life (Porter *et al*., 1998). Moreover, and on the other hand, acute invasive procedure prime preterm infant biobehavioural response systems to subsequent handling (Porter *et al*., 1998), even routine handling before a skin-breaking procedure leads to similarly heightened responses. (Grunau *et al*., 2006)

•**Slowed recovery:** It has been shown recently that when behavioral responses were recorded over a 20 minute period during recovery from heel lance, preterm infants showed sustained body movement responses indicative of stress that lasted 4-18 minutes after the last contact of the laboratory technician (Morison *et al*., 2003).

•**Behavior and cognition:** It was found also that later in childhood, behaviorally from 3 to 9 years, extremely preterm children, even those with normal intelligence showuncertainty and anxiety when dealing with novel cognitive challenge.(Whitfield *et al*., 1997)

b.Long-term behavioral sequelae related to perinatal complications

1-Self-destructive behavior

2-Drug abuse

Administration of multiple doses of opiates, barbiturates and nitrous oxide to mothers during delivery were found to increase the occurrence of subsequent opiate or amphetamine addiction in the offspring as compared to when no drug was given (Jacobson *et al*., 1990).

c.Long-term neurobehavioral effects related to perinatal complications

Ex-premature infants often have more educational, behavioral and emotional difficulties during school age and adolescene as compared to their ex-full term peers (Hack *et al*., 1994).

Assessment of neonatal pain

Components of neonatal pain assessment tools

A.Behavioral indicators

a. Facial expression: Facial expression is generally considered the most sensitive indicator of pain in neonates (Grunau *et al*., 1990). An example of a unidimentional instrument focusing on facial expression is the "Neonatal Facial Coding System" (NFCS), which assesses ten discrete facial actions, either from videotaped material or from bedside observation (Grunau *et al*., 1998).

b. Body movement and muscle tone: One drawback is that it may be misleading in the immobile painful infant (Van Dijk *et al*., 2004). Posture is assessed by observation and tone by touching the neonates arm or leg.

c. Crying: Pain instruments assess crying by either scoring intensity or by scoring frequency.

d. Behavioral state/sleep pattern: The PIPP includes behavioral state because sleeping infants exhibit fewer sustainable responses, therefore score higher on this item than those awake, which corrects for the less vigorous response to acute pain when asleep.

e. Consolability: Consolability, which assesses if an infant is condonable and how long it takes to calm the infant is included in 3 of the neonatal pain instruments: the Behavioral Pain Score (BPS), the Bernese Pain Scale for Neonates (BP NS) and the Echelle Douleur Incomfort Nouveau - Ne (EDIN) (Cignacco *et al*., 2002).

f. Skin color: Four instruments use skin color as indication for pain:
1- Pain Assessment Tool (PAT).
2- Distress for Ventilated Newborn Infant (DSVNI).
3- Bernese Pain Scale for Neonates (BPNS).
4- Nepean Neonatal Intensive Care Unit Pain Assessment Tool (NNICU PAT).

B.Physiological indicators

Heart rate, blood pressure, oxygen saturation and breathing (frequency or ir regularity) are the most frequently used physiological indicators of pain (Sweet and McGrath, 1998).

- There are 10 pain instrument tools include physiological indicators. There are multiple draw bakes in using these physiological indicators in pain assessment.

1- Deviations in these physiological parameters may be caused by underlying illness making them less specific for pain.
2- Daily medical interventions aim at keeping heart rate, blood pressure and oxygen saturation at acceptable levels without treating pain .
3- Physiological indicators are not specific for pain in the postoperative setting.
4- Increases in heart rate due to acute pain may be short lasting and therefore remain unnoticed. (van Dijk *et al*., 2001)

C. Biochemical indicators

a. Catecholamines, glucagon and insulin: (Anand *et al*. 2000) demonstrated a marked increase in adrenaline, noradrenalin and glucagon with a reduction in insulin secretion; these changes were ablated by preoperative treatment with fentanyl.

b. Endorphins: (Anand and Hickey 1987) found that CSF levels of β endorphins were increased markedly in newborns with apnea of prematurity, infection or hypoxemia.

c. Cortisol: The most important stress hormone secreted in response to pain and stress, it will be discussed in detail in next section.

d.Malondialdehyde (MDA): There is significant relationship between procedural pain and detectable oxidative stress in neonates which is evaluated by measuring uric acid and Malondialdehyde (MDA) concentration in plasma.

Pain asssessment instruments

- Selection of an appropriate clinical pain assessment method should be based first on the developmental age of the infant and second on the type of pain or medical condition for which specific assessment tool exist e.g. for procedural or post-operative pain.
- The NIPS, PIPP, CRIES and the NFCS were selected by an international consensus meeting group. The first two have been validated for acute procedural pain, the CRIES primarily for post-operative pain. The NFCS is primarily used in studies which use video material to assess the NFCS during painful procedures (Anand, 2001)**.**

Management of pain in neonates

- Reduction of painful events:
- The most effective way of reducing minor procedural pain in the neonates is to reduce the number of procedures performed.
- The most effective way of reducing minor procedural pain in the neonates is to reduce the number of procedures performed (Gibbins *et al*., 2003).

A.Non-pharmacological pain prevention procedures

a. Breastfeeding

Breastfeeding was associated with reduction in changes in heart rate, duration of crying,percentage time crying and improvement in validated and non validated pain measures when compared to placebo /no intervention /positioning in neonates (Shah *et al*., 2006).

b. Non-Nutritive sucking (NNs)

The pacifying effects of non-nutritive sucking were clearly shown in multiple studies that reported decreased crying, lower heart rates and increased oxygenation in term and preterm neonates during painful procedures like heel sticks and venipuncture.

c. Kangaroo care

d. Facilitated tucking

In tucking, the nurse or parent holds the infant by her or his hands in a side-lying, flexed fetal-type position, offering support and skin contact (Axelin, 2010).

e. Swaddling

Swaddling involves wrapping the neonate in a fabric cloth. swaddling after a painful intervention is associated with clear reduction in the heart rate and it also has an effect on oxygen saturation for all age groups(ACignacco *et al*.,2001).

f. Positioning

Laying the neonates in a prone position is a frequent measure in everyday practice as it is expected that the counter pressure of the mattress will relieve the pain being experienced.

Figure 1. Facilitated tucking

Figure 2. Swaddling

g. Olfactory and multisensorial stimulation

A familiar odor might be effective in relieving distress associated painful stimuli in pre-term infant like odor of breast milk (Cignacco *et al*., 2007).

h. Music

Beneficial effects of music on pain response are lowering of heart rate and rise in oxygen saturation and a reduction in excitation state in infants more than 31 weeks of gestation. (Hartling *et al*., 2009).

B.Pharmacological pain prevention methods

a. Sucrose

Small amount of sweet solutions placed on the neonates tongues have been shown to mediate an increase in endogenous opioid release, reduce the procedural pain and minimize crying following the procedure (Stevens *et al*., 2004). Sucrose should be used in conjunction with environmental and behavioral measures to relieve pain in the following doses:

- **24-26 week gestation:**0.1 ml.
- **27- 31 week gestation:**0.25 ml.
- **32- 36 week gestation:**0.5 ml.
- **37 week gestation:**1 ml.

b. Paracetamol and other NSAIDs:

Paracetamol (acetaminophen) acts primarily by inhibiting the COX enzymes in the brain and has been well studied in the newborns, particularly for mild procedural pain or fever reduction after immunizations.

c. Opioids:

Opioids inhibit afferent pain in the spinal cord and activate descending inhibitory pathways. Due to their action in other opioid receptors they can cause respiratory depression sedation, ileus, urinary retention, nausea and vomiting and physical dependence (Bellur *et al*., 2005).

1- Morphine

(Chay *et al*., 2002) demonstrated that a concentration of morphine of 125 ng/ml was necessary to produce adequate sedation in 50% of newborns studied at term and premature.The recommended doses for the neonatal period are intermittent intravenous administration of 0.05 to 0.20 mg/kg per dose up to every 4 hours. Continuous administration for newborns at term of 5 to 20µg/kg /h and 2 to 10 µg/kg/h in premature neonates (Taddio, 2002).

2- Fentanyl

Fentanyl is commonly used in neonatology for its capacity of providing fast analgesia with hemodynamic stability (Aranda *et al*., 2005). It has faster onset of action and shorter duration (less than 2 hours) than morphine its T½keo is 6.4 minutes and a context sensitive half life of 260 minutes after 4 hours of infusion. (Stoelting and Hiller, 2006)

The recommended doses for the neonatal period are:

- Intermittent intravenous administration of 1-4 µg/kg every 2-4 hours.
- Continuous intravenous administration in newborns at term of 0.5-3µg/kg/hour and 0.5-2µg/kg/hour in premature neonates the down side of the continuous infusion is the fast development of tolerance with the need of increasing doses to achieve the desired analgesia (Guinsburg, 1999)
- Fast administration of high doses (above 5 µg/kg) could cause muscle rigidity especially in the thorax hindering ventilation and inducing laryngeal spasm in newborns (Greco and Berdo, 2000).

d. Sedatives:

Midazolam and lorazopam are used extensively in neonates but diazepam is used infrequently because of its limited metabolism in neonates (Jacqz *et al*., 1994).

e. Narcotics:

Barbiturates such as phenoborbital and thiopental have been used extensively in neonates for sedation and seizure control. Phenobarbital is often used in conjunction with opioids to provide sedation, and for reducing excitability in the neonatal abstinence syndrome (Osborn *et al*., 2002).

Despite its theoretical advantage as a potent analgesic, sedative and amnestic agent, Ketamine has been minimally studied in neonates; thus, it should be used mostly in approved research protocols (Soriano *et al*., 2005). Similarly, Propofol has gained increasing popularity as an anesthetic agent for neonates (Davis *et al*., 2001)

f. Local anesthetics:

Local anesthetics effectively reduce procedural pain in neonates. Injectable lidocaine and topical creams have both been studied in various neonatal population. Lidocaine is used commonly for dorsal penile nerve block in circumcision, but a head-to-head comparison reported ring block to be more effective than either dorsal penile block or topical anesthetics (Lander *et al*., 1997). Lidocaine infiltration however is not effective for lumber puncture in neonates (Porter *et al*., 1991). Complications of therapy with lidocaine include case reports of seizures and changes in brain stem auditory response with lidocaine injection. Various topical anesthetics have been tried in neonates with variable success. The first of these is Eutectic Mixture of Local Anesthetics (EMLA) cream was studied extensively in neonates for procedural pain. (Taddio *et al*., 1998)

Although newer agents have a shorter onset of action and may be more effective e.g. the pain from heal prick the most skin breaking procedure in neonates is not affected by EMLA cream (Stevens *et al*., 1999) although multiple studies have shown its efficacy for venepuncture, lumbar puncture or immunization, it was less effective than sucrose for venepuncture or lidocaine blocks for circumcision (Anand and Hall, 2006) complications of topical anesthetics include methoglobinemia from prilocaine component if EMLA cream is not applied correctly, or transient skin reactions from various agents.

Another remedy of local anesthetics used for pain relief is the novel tetracaine patch whose efficacy was tested by (Long *et al*., 2003) in 32 newborn infants (32 to 42 weeks gestational age), they found that 14 out of 15 tetracaine patch treated infants (93%) had little or no pain in response to venepuncture after applying tetracaine containing patch 30 minutes before the procedure.

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