HOW DOES EARLY LIFE EXPERIENCE AFFECT ADULT PERCEPTION?

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ABSTRACT

Pain in neonates is now an irrefutable fact and recent studies suggested different methods to measure it although the difficulties to adopt them to the clinical routine. Short and long-term effects of neonatal pain and stress in neurodevelopment have been demonstrated by several studies, with outcomes varying from hyperalgesia and sensitization to adult pathologies such as depression, anxiety and Alzheimer disease. The impairment of peripheral and central nociceptive pathways caused by early life experience encompasses four main processes: injury leading to pain, cell death, inflammation and neuroplasticity. Therefore, to prevent or minimize these outcomes, clinical routine must be aware of this essential matter. Particularly for newborns that demand intensive units care and repeated painful procedures there are recent attempts regarding this concern. The widely use of sucrose analgesia prior to painful procedures did not prevent hyperalgesia and should not be used as a single analgesic. Other strategy, as the use of environmental care, has shown better results with reduction in neonatal stress and superior brain maturation. Hence, further studies in the area of neonatal analgesia are required to implement best practices in the medical routine and prevent the consequences of early life pain experience.

KEY-WORDS: Newborn Pain, Nociceptors, Neuronal Plasticity, Analgesia, Time

1. INTRODUCTION

Neonatal pain is a highly discussed topic in both neuroscience and pediatric areas and its importance has increased since studies have proved that not only neonates can feel pain but also that this experience might lead to short- and long term effects, including adult pathologies[1,2]. Rodent and human experiments associated with clinical observations have suggested that early life pain/stress experience, principally in very preterm newborns, may lead to alterations in the function and structure of the rapid developing brain[3].

Hyperalgesia, pain sensitization, impaired cognition and motor function, depression and anxiety are examples of neurodevelopmental changes that are suggested to be caused by neonatal pain/stress[4]. The mechanisms and the reasons for this occurrence are poorly comprehended, however, recent studies highlight evidences of neural plasticity related to the development of the nociceptive pathways and pain processing[5,6].

Although long-term effects of neonatal pain exposure on neurodevelopment need further investigation, the proper management of painful procedures during neonatal period should be applied in order to prevent or minimize short and long-term outcomes in both psychological and structural neural development, as the evidences have shown[7]. Recent studies in neonatal pain management have demonstrated promising results in terms of improved maturation and development of the brain and better long-term effects when using techniques to reduce pain in neonates, such as anaesthesia, sucrose administration or parent training[3,5].

2. MATERIAL AND METHODS

An integrative literature review was conducted by four independent authors on the following databases: PubMed, Lilacs and Scielo. One filter was applied: 'last five years'. The keywords used were selected according to MESH and BVS descriptors, adapted to each database and combined (newborn pain AND pain measurement AND neuronal plasticity AND analgesia AND nociceptors AND time).

In order to identify further papers, authors searched manually the list of references from the papers selected and other databases, such as Uptodate, Cochrane and Pubmed (without the filter specified).

From the survey of the publications in the databases described, the pre-selected publications were identified, obtaining 1366 articles. From the exclusions by title, abstract, full text and duplicate articles, a more restricted selection was made, adding to it the studies selected from the manual search. Thus, 57 articles were obtained to compose the final sample. Through the thematic axes compiled in the synthesis matrix **(Table 1)**, it was possible to approach the topics involved in the subject studied, debating what has been presented on the subject in the last five years.

Table 1: Synthesis of the main data collected

Descriptors	Authors and years of publication	Clinical study Design	Main results
Newborn pain AND Nociceptors	Liu, X., Green, K. J., Ford, Z. K., *et al. (2017)*	Clinical trial	This study suggest that the growth-hormone (GH) may be associated with pain modulation of the neonate;
	Li, J., Kritzer, E., Craig, P. E.,	Clinical trial	Surgical incision during neonatal period evokes long-term alterations to

	& Baccei, M. L. (2015)		inhibitory and excitatory synaptic circuits on mices;
	Jankowski, M. P., Ross, J. L., Weber, J. D., *et al. (2015)*	Clinical trial	Perypherical fibers injuries during early-life impair pain perception and sensorial function during adulthood;
Newborn pain AND neuronal plasticity	Schwaller, F., & Fitzgerald, M. (2014)	Literature review	Highlight new perspectives to future research at the comprehension of the peripherical and central pain mechanisms;
Newborn Pain AND Analgesia	Lemus-Varela (2014)	Literature review	Painful procedures are commom in neonates, but analgesic therapy is not given in most of cases;
	Hall (2014)	Literature review	It is important to assess pain in newborn and to standardize prevention techniques to reduce neonatal painful procedures;
	Kanwaljeet (2017)	Literature review	Breastfeeding, non-nutritive sucking, swaddling or facilitated tucking, skin-to-skin contact and sensorial saturation are the nonpharmacological approaches that can effectively reduce pain and discomfort from routine care measures and minor procedures in both preterm and term neonates;
	Stevens (2013)	Literature review	Sucrose is effective for reducing procedural pain from single events such as heel lance, venipuncture and intramuscular injection in both preterm and term infants, with no serious side effects or harm related;
	Carbajal (2008)	Cohort study	Further follow-up studies are needed to determine if there are significant long-term effects of neonatal sedative or analgesic drugs to identify efficacious and well tolerated analgesic treatments and to improve analgesic provision in the infant population;
	Carbajal (2015)	Cohort study	Opioids are the most effective therapy for moderate to severe pain in patients of all ages and morphine and fentanyl are commonly used opioids in neonates;
	Victoria (2015)	Clinical trial	Analgesia for early-life pain prevents adult hyposensitivity to acute anxiety and stress-provoking stimuli and increased vulnerability to chronic stress, and have important clinical implications for the management of pain in infants;
Newborn pain AND Time	Beggs (2014)	Literature Review	Neonates do not have the pain inhibitory system fully developed which leads to an inhanced response to noxious stimuli and the potential to long-term impairment at the development of pain responses and autoimune responses;
	Vinall & Grunau (2014)	Literature Review	Neonatal exposure to stress and pain, particularly preterms infants are associated to altered brain development, stress hormone levels and poorer behavioral development;

Details of the search strategy are fully described on the Figure 1 below.

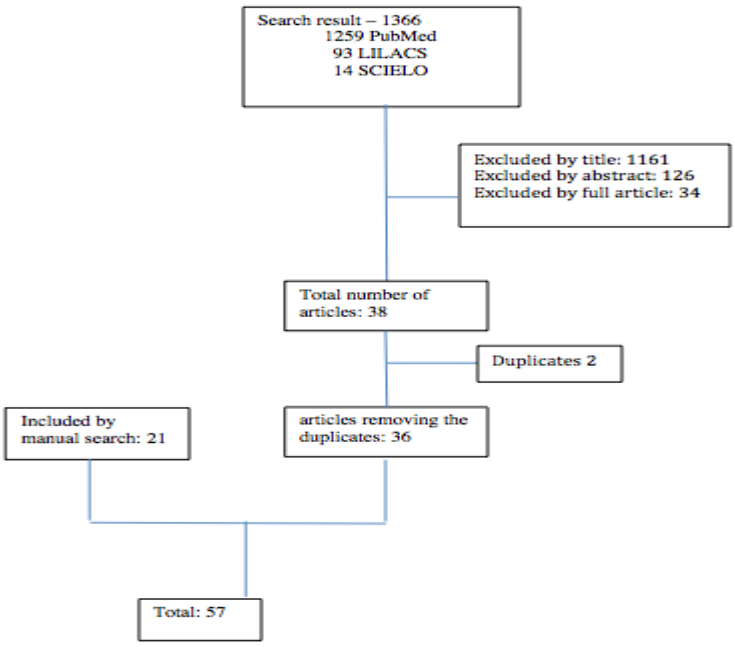

Figure 1: Details of the search strategy.

3. RESULTS AND DISCUSSION

Definitions

What is pain?

The official pain definition of the International Association for the Study of Pain (IASP, 1979) is: "an unpleasant sensory and emotional experience associated with actual or potential damage, or described in terms of such damage"[8,9]. Pain can result from both physical and psychological responses to injury. Therefore, pain is a subjective experience that engages a multidimensional

response[10].

The concept of pain response encompasses four categories: nociception, perception, modulation and behaviour. Nociception is the component that emits signs, via peripheral transducers, that leads to the experience of pain. These transducers are combined with C and Aδ fibers and are activated by stimuli that have the potential to cause tissue lesions. The activation of these fibers generates activity at the dorsal horn of the spinal cord that relays to several areas of brain, via ascending tracts, leading to different perceptions of pain[9,11]. Modulation of pain is due to descending tracts with both inhibitory and facilitatory transmitters involved in these pathways. Behaviour is the personal response to pain, which is related to subjective pain experience[12,13].

What is neonatal stress and pain?

According to the neonatal pain control group of the Newborn Drug Development Initiative, stress is defined as "an actual or perceived threat that leads to a disturbance of the dynamic equilibrium between an organism and its environment"[14]. Therefore, neonates, especially those admitted to the neonatal intensive care units (NICU) may experience a hostile environment and undergo repeated painful procedures that lead to a response to various stress stimuli. This response is due to individual's perception of the environment and elicits changes in four primary domains: autonomic, immunological, endocrine and behavioural[14].

Early stress experience, such as maternal separation, severe illness and repeated medical interventions may lead to sensitization and neuroplasticity which may be related to adult disorders such as depression, post-traumatic stress and fibromyalgia[15]. One study, by Aisa et al 2009, shows that long-term exposure to neonatal adverse events deregulates the hypothalamic-pituitary-adrenal (HPA) pathway increasing the susceptibility to psychopathology during adulthood[1]. One of these events is maternal separation during the postnatal period, which can cause augmented stress reactivity in adults in both neuroendocrine and behavioural aspects. This behavioural consequence is a result of increased glucocorticoid levels that can also lead to memory impairments in a long-term exposure. In addition, this study showed that early-life stress affects cholinergic neurons allowing them to be more vulnerable to later insults and as a consequence may contribute to cholinergic and cognitive deficits in the Alzheimer disease[1]. Aisa et al. 2008 in another study demonstrated in rats that maternal separation during the postnatal period increases the probability of developing depression-like syndrome in female adult rats and anxiety in male adult rats. These adult conditions as mentioned before by other studies are related to high glucocorticoids levels since the effects were reversed by mifepristone, which is a glucocorticoid antagonist[2].

Contrary to what researcher used to believe, historically, the human fetus by the second half of gestation has a well differentiated functional sensorial system and mechanisms to process pain[16,17]. Thus, preterm and term neonates are also capable of experience stress and pain when exposed to noxious stimuli[1,18]. Peripheral and central nociceptive pathways are involved in pain response during the neonatal period, however the nature of the reaction to painful stimuli diverges with age[5]. In early life, descending pathways are mostly excitatory, and inhibitory mechanisms are later to develop[5,19]. Moreover, there are differences in sensory fibers between neonates and adults with outcomes for pain responses. Aβ myelinated fibers, which reacts to light touch, extend to laminae I-II of the dorsal horn in neonates, while in adults restrict to laminae III-IV. Also, these fibers in newborns connect with A-delta myelinated and C unmyelinated fibers in order to respond to painful stimuli[20].

How does pain affect neonates?

Pain in neonates has short- and long-term effects, as several studies have shown. One study reports alterations of cerebral pain processing in 11-16 years ex-preterm children, such as pain sensitivity growth and greater brain activity related to pain in insula, primary somatosensory and anterior cingulate cortices areas[21]. Another study shows that infants who needed several heel lances in the first 24-36 hours of life is presented clinically with hyperalgesia following venipuncture compared to children who had not painful procedures while newborn infants[22].

Distress related to needle-stick procedures can lead to phobic effects[3] making later practices difficult. Additionally, altered levels of neural activity, which is a consequence of pain, may cause impaired central nervous system development, sensitization of pain pathways with subsequent hyperalgesia[23].

Children neurodevelopment is also affected while a huge exposure to pain in procedures has been correlated to altered growth, damaged structure of corticospinal pathway, decreased cognitive and motor scores and delayed maturation of white matter and subcortical grey matter[5,9].

Nociceptive pathways development

Injury Leading to Pain

The development of sensory pathways in spinal cord and other parts of Central Nervous System (CNS) is dependent on activity. Consequently, injury in neonates may lead to changes in somatosensory processing, synaptic development and pain behaviours.

Nociception maturation starts from early life experience and the quality of response to noxious stimuli is age-dependent. For example, hyperalgesia and allodynia, clinically noticed after subsequent damage tissue, occurs in all ages, but the mechanism and duration of these responses changes with neuronal development[6].

Walker et. al, 2002 point out that blood sampling via repeated heel prick causes hyperalgesia in the damaged tissue area and increase in abdominal skin reflex after primary visceral disease or surgery. Whilst, Duan et al. (2014) and Petitjean et al. (2015) suggest that inhibitory interneurons present in the CNS - expressing either dynorphin or parvalbumin proteins - may have the ability to inhibit the pain sensation during a innocuous mechanical stimuli by inactivating ascendent projective neurons. Thus, pharmacogenetic suppression of these interneurons could lead to hypersensitivity to harmless mechanical stimuli, such as allodynia[24,25]. Additionally, Jie Li and Mark L. Baccei

(2016) advocated that tissue damage on infants evokes the production of long-term potentiation on adult nociceptive pathways and such metaplasticity may be correlated to an increase of ascending nociceptive transmission to the adult brain enabling the development of chronic pain[26]. They also reported that surgical incision during neonatal period lead to long-term impairment of spinal nociceptive circuits (inhibitory and excitatory synapses), intensifying the ascending nociceptive pathways to the areas of the brain that modulates the pain in adult rats[27]. Jankowsky, M et al (2014) pointed out that early-life injury of the peripheral pain fibers impair pain perception during adulthood. However, if the injury occurs after the complete maturation of these fibers, no long-term effects could be observed[28].

Inflammation

Sensory neurons in neonates express a notable acute response to inflammation in peripheral tissue. This response and long-term processing to pain are dependent on the quality and quantity of the inflammatory stimuli. Neonatal animals are different from adult animals in so far, as after an acute inflammation they present an increase in the primary afferent terminal within the dorsal horn[29].

Benatti et al., 2009 showed in experiments with neonatal rats that inflammation activates central nervous circuits affecting the development of pain pathways depending on the type of inflammatory stimulus. For instance, if it is a long-term local insult during early life, rats will develop higher pain sensitivity and responses to thermal pain[30].

Recent studies suggest that the growth hormone (GH) may be related to pain modulation. Liu, Xiahua et al (2017) observed that GH may lead to a certain level of hyper-responsiveness to pain induced by inflammation during neonatal period, suggesting that this mechanism is related to the upper regulation suppression of the insulin-like growth factor 1 receptor (IGFr1) in the dorsal root ganglia[31].

Cell Death

Activity of the neuronal system in neonatal brain is related to cell survival and regulator factors in brain development. Additionally, one experiment with rats shows that inflammatory pain causing neuronal cell death is regulated by development. Follow-up studies presented that ex-preterm neonates presented cognitive deficits, needing greater health care and special education[23].

Anand et al., 2007 demonstrate that the main brain areas affected with cell death by subsequent pain exposure in post-natal rats are cortical, thalamic, hypothalamic, amygdaloid, and hippocampal areas. Also show that these effects are bilateral despite a unilateral stimulus. These results were inhibited in rats treated with ketamine, which has analgesic properties, can blockade excessive pain stimuli and anti-inflammatory effects. Additionally, this study emphasizes that the brain areas, such as thalamic nuclei and habenula, which showed low NMDA receptor activity did not show the same protective effects of ketamineadvocating the role of these receptors in neuronal cell death. Furthermore, another study from Klein et al., 2007 points out that decreased doses of the NMDA-receptor antagonist ketamine avoided increased pain perception after a high-frequency nociceptive input[32].

Neuroplasticity

Brain development is associated with genetic and environmental factors, which include stress, emotional aspects, medications and sensorial stimuli. The neonatal period is characterized by abundant plasticity and reorganization of the neural system, which a great number of newborn may demand invasive procedures[30,33]. There is clinical and experimental evidence suggesting that peripheral injuries associated with pain experience and inflammation may lead to changes in the function of central nervous system which may have influence in the nociceptive processing, as detailed below[5,34] .

According to Géranton (2012), epigenetics mechanisms will be soon correlated to memory formation involved in pain processing. Adult animals that suffered leg injury during neonatal period present upward regulation of GABA, histamine, serotonin, cholecystokinin and neurotensin systems on the ipsilateral dorsal horn. However, it is not certain how epigenetic changes could lead to changes in pain modulation[35].

Experimental Evidence

Several animal models of early life pain experience have been performed to discover how it affects the developing central nervous system in terms of pain patterns as presented in the Table 2 below (7). These studies tested different types of pain stimuli in neonates comparing to adult's rats, such as neonatal hind paw plantar incision, full thickness skin wound, repeated needle prick, and peripheral nerve injury, as shown in the following table **(Table 2)**.

Table 2: Consequences of pain in early life

Neonatal injury	Effects on adult baseline sensitivity
Hindpaw plantar incision	Generalized baseline hyposensitivity (F. Schwaller & S.M. Walker, pers. comm.)
Laparotomy (P0)	Generalized baseline hyposensitivity (Sternberg *et al.*, 2005)
1 mm × 1 mm hindpaw skin removal	Behavioural hypersensitivity and hyperinnervation at site of injured skin (Reynolds & Fitzgerald, 1995; Beggs *et al.*, 2012a)
Four needle pricks daily between P0 and P7	Thermal hyperalgesia (Anand *et al.*, 1999)
Hindpaw carageenan (CAR) or complete Freunds adjuvant (CFA) injection	Generalized baseline hyposensitivity (detectable after P34) (Ren *et al.*, 2004).

Schwaller, F., & Fitzgerald, M. (2014). The consequences of pain in early life: injury induced plasticity in developing pain pathways. European Journal of Neuroscience, 39(3):344-352.

Overall, the experimental evidence of these studies is that tissue harm, peripheral nerve damage or inflammation in early life period has short and long-term neural development effects, causing changes of the pain pathways patterns and significant spinal cord, peripheral and behavioural modifications related to pain processing[29]. For example,

neonatal nerve damage can lead to a considerable neuronal death in the posterior first weeks and mechanical hypersensitivity in adulthood.

Li and Baccei (2016) observed that surgical incision - tissue damage - during neonatal period evokes long-term potentiation (LTP) at primary afferent synapses in projection neurons in adult animals, which are essential for both pain perception and development of nociceptive spinal system. This persistent LTP during neonatal period is a factor that contributes to an amplification of the ascending nociceptive pathway transmission to the CNS and a great response to pain in adults who are exposed to subsequent tissue injury[26].

A recent study by Duerden et al. (2018) shows that early exposure to pain, especially in extremely premature newborns - which pain modulation systems have not reached maturity - is associated with certain changes in thalamus, thus in motor and cognitive function, such as: disruption of thalamic metabolic growth, impaired maturation of the thalamocortical pathway associated with decreased volume in the somatosensory area of the thalamus[36]. Future assessment of neonatal pain should focus on how pain modality, location and magnitude may impact the adult phenotype, and details on how tissue injuries modulate peripheral and central pain mechanisms[7].

How to measure pain in neonates?

Pain is always subjective, so it is difficult to measure it during childhood and even more difficult to perform it in newborns. In addition, rapid changes in brain development during neonatal period make this assessment even more challenging[19,37]. However, there are different methods to evaluate pain in neonates and its use was strongly recommended by American Academy of Pediatrics and by international researcher, including International Evidence-Based Group for Neonatal Pain[37]. Some of these are detailed in **Tables 3** presented below.

Table 3: Tools available to measure pain in neonates

Tools	Variables included	Utility
Premature infant pain profile (PIPP)[24]	Gestational age, behavioral state, heart rate, oxygen saturation, brow bulge, eye squeeze, nasolabial furrow	Procedural and postoperative pain
FLACC (25)	Face, legs, activity, cry, consolability	Procedural and postoperative pain
COMFORT scale (behavioral and physiological parameters)[26]	Alertness, calmness, respiratory distress, movement, muscle tone, facial tension, blood pressure, heart rate	Pain and sedation in NICU
COMFORT behavioral scale[27]	Alertness, calmness, respiratory response (ventilated) or crying (not ventilated), movement, muscle tone, facial expression	Postoperative pain in NICU
Neonatal Infant Pain Score (NIPS)	Facial expression, crying, breathing patterns, arm and leg movements, arousal	Procedural
Neonatal Facial Coding System (NFCS)	Facial actions	Procedural
Neonatal Pain, Agitation and Sedation Scale (N-PASS)	Crying, irritability, behavioral state, face expression, extremity tone and vital signs	Procedural, postoperative, and ventilated
Cry, Require oxygen, Increased vital signs, Expression, Sleeplessness (CRIES)	Crying, facial expression, sleeplessness, requires oxygen to stay > 95%, increased vital signs	Postoperative
Douler Aigue Nouveau-né scale	Facial and limb movements and vocal expressions	Procedural pain
Behavioral Infant Pain Profile	Behavioral state, facial expression and hand movements	Acute pain

Since neonates are not able to self-report, the measurement of pain must be based on behavioural aspects and associated variables. The recent methods to evaluate pain are divided in one-dimensional (contemplate one behavioural aspect of the pain) and multidimensional tools (include multiple characteristics of pain response, such as physiological and behavioural aspects)[38]. However, recent review studies emphasised that there is no pain scale superiority indicated to assess neonatal pain[37]. Amongst various pain scales, the most used are shown on the table below.

Fournier-Charrière et al., 2012 report a pain scale in attempt to face this issue from ages 0-7 in the emergency department[39]. The scale named EVENDOL, which means Evaluation Child Pain, covers different types of pain, ages, stress levels and is not subject to observer variations. Items assessed in this scale are facial, vocal, social and motor behavior, which can be scaled from 0 to 3 (0=absent, 1=weak or transient, 2=moderate or present in half of the time, 3=strong or present almost all time)[39].

A recent study in neonatal pain, using fMRI, concluded that the cortical areas and sensory components that are activated during noxious stimuli are exactly the same in different ages, suggesting that pain processing and perception are similar in both neonates and adults[40]. However, in clinical situations these assessment tools are not easy to apply due to the high cost of the technologies and mainly because they are not convenient for routine medical practice, since it involves numerous procedures, a long time period and excessive manipulation of the neonates.

Prevention and management of neonatal pain

It is consensus among studies that painful procedures are common in neonates, especially in those in the NICU. However, analgesic therapy is not given in most of cases. According to Lemus-Varela, 2014, it is estimated that everyday neonates are exposed from 0 to 53 procedures, and even when almost a quarter of are reported as very painful, a third does not receive any analgesia. A large prospective French Study has confirmed the majority presence of painful procedures, despite of the small analgesic therapy and provided a great picture of the high prevalence of untreated neonatal pain[41]. Lima, 2012, Lemus-Varela and Hall (2014) emphasize the importance of assessing pain in newborn and the standardization of prevention techniques to reduce neonatal painful procedures, but also point out that pain assessment scales are not used in most of institutions, as it is

a difficult topic to teach, often vulnerable to individual interpretation that can lead to conflicts in the NICU care. Caetano, 2013, reiterates the need to empower professionals on this matter[42,43].

The analgesic therapy is divided into non-pharmacological and pharmacological types and the use of analgesics has precise indications but also important limitations and adverse effects need to be considered. Stress management should begin in the first contact with the health care institution, including maternal contact, stimuli reduction and the implementation of intervention reduction protocols[44]. It is important to emphasize that the therapy is done in steps according to the intensity of the pain (see **Table 4**) and that in most settings where there is a need to accelerate the steps of intervention, it is important to note that less invasive interventions are still provided.

Table 4. Steps for neonatal analgesia

Step 6	Deep sedation/ analgesia or general anesthesia
Step 5	Local anesthetics: subcutaneous infiltration of nerve blocks
Step 4	Slow intravenous infusion of opioids
Step 3	Acetaminophen or NSAIDs
Step 2	Topical anesthetic cream or gel
Step 1	Pacifier, sucrose, kangaroo care, massage, sensorial saturation
Baseline	Avoid painful procedures , physical handling

According to Kanwaljeet, 2017, breastfeeding, non-nutritive sucking, swaddling or facilitated tucking (defined as gently maintaining the arms and legs in a flexed position), skin-to-skin contact[45] and sensorial saturation (use of touch, massage, voice and smell) are the nonpharmacological approaches that can effectively reduce pain and discomfort from routine care measures and minor procedures (eg, heel stick) in both preterm and term neonates. However, the former approach is labour-intensive and it is difficult to define the proper amount of stimulation to be used. The first one is a developmentally superior alternative to oral sucrose or glucose for pain control. Nonpharmacologic approaches are generally more effective when used in combination than when used alone[49]. Another study by Grunau, 2013 recommended the use of an environmental care and the presence of the parents during a painful procedure, which have shown a decrease in neonatal stress, improved brain maturation and better white matter connectivity[3].

Oral sucrose and other sweet-tasting liquids are among the three types of pharmacological therapy as local analgesia, including topical anaesthetics and lidocaine and systematic analgesia, including opioid therapy. According to Stevens, 2013, sucrose is effective for reducing procedural pain from single events such as heel lance, venipuncture and intramuscular injection in both preterm and term infants, with no serious side effects or harm related. Further investigation is needed because remains unclear whether sucrose suppresses the neurophysiologic responses to pain and whether electroencephalographic (EEG) and electromyographic (EMG) responses are relevant for the study of neonatal pain[46,47].

Topical local analgesics reduce procedural pain in children, however studies are still limited and inconclusive. Lidocaine is injected locally to reduce the pain associated with venous or arterial puncture, percutaneous venous or arterial catheter placement, LP, and circumcision and is also used during surgical operations to reduce the postoperative hyperalgesia and the need for postoperative analgesia. Systemic pharmacologic agents reducing neonatal pain and stress include nonopioid analgesics (eg, acetaminophen and ketamine), nonsteroidal anti-inflammatory agents, and opioid analgesics (eg, morphine, fentanyl, oxycodone, and methadone). Studies have shown that general anaesthetics may cause accelerated apoptosis and other adverse morphologic changes in neurons of the developing brain. Another significant evidence however shows that providing effective analgesia, sedation, and anaesthesia would seem to be more important than concern over neurotoxicity[49].

Opioids are the most effective therapy for moderate to severe pain in patients of all ages and morphine and fentanyl are commonly used opioids in neonates[48], but the benefits of opioid therapy as injectable lidocaine needs to be balanced by its adverse effects. Victoria, 2015, suggest that analgesia for early-life pain prevents adult hyposensitivity to acute anxiety and stress-provoking stimuli and increased vulnerability to chronic stress, and have important clinical implications for the management of pain in infants. Whether it is an effective and safe neonatal analgesic in these clinical settings remains under active investigation and further follow-up studies are needed to determine if there are significant long-term effects of neonatal sedative or analgesic drugs to identify efficacious and well tolerated analgesic treatments and to improve analgesic provision in the infant population[41].

4. CONCLUSION

Clinical practice should be based on early pain experience outcomes. Pain is determined by genetic background and environmental factors, which means that early life noxious experiences may lead to changes in adult response to pain. This fact is especially relevant when considering premature infants who often seek intensive units care and repeated noxious procedures. Therefore, newborn infants should be afforded special attention regarding painful procedures.

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