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CURTAILING PROCEDURAL PAIN / STRESS IMPACT IN EXTREMELY PREMATURE INFANTS: CURRENT PRUDENCE AND CROATIAN CONSUETUDE

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For a long time belief persisted that premature infants do not experience pain. Extremely premature newborns are exposed to number of diagnostic and therapeutic interventions during their stay in neonatal intensive care units. That time coincides the time of rapid brain development, when transitional neuronal structures are particularly vulnerable. Repeated painful and stressful procedures have proven impact on brain development of premature infant. As long-term effects of procedural pain and stress were recognized efforts of reduction became an imperative of neonatal medicine. We present non-pharmacological and pharmacological methods of procedural pain control; action, known side-effects and efficacy. We also refer to practice of high level neonatal intensive care units in Croatia. Non-pharmacological methods such as non-nutritive sucking, facilitated tucking, swadling, parental involvement, and others, have proven efficiency in pain control of many procedures causing mild pain. In combination with topical anesthetics and sweeteners they are effective in procedures of moderate intensity. Non-farmacologicala methods affect transmission of painful stimuli and as sweeteners dampen behavioral response. Among drugs opioids are far most effective during severly painful procedures and side-effects should be balanced with impact of pain and stress. Eye examination for retinopathy of prematurity is an inevitable procedure stressful at the very eye drops application. It demands to be marked since only opioids have proven absolute efficacy which should be kept in mind with ventilated and haemodynamically unstable patients. Non-pharmacological methods as well as topical anestetics are uneffective when heel lance for blood sampling is performed. Overall, awareness of pain and stress in Croatian high level units exists, but recognition of pain and stress malevolence and action in terms of prevention are still insufficient, especially in terms of mild to moderate intensity procedures.

Key words: premature infant, newborn infant, pain, pain management, analgesia, retinopathy of prematurity

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INTRODUCTION

After birth, very premature infants spend weeks, sometimes months, in neonatal intensive care units (NICU). During that time they undergo many diagnostic interventions and interventions of treatment and care. For a long time possibility of premature infants to experience pain and stress was not aknowledged in NICU. When their capacity to feel and experience stress was recognized focus arised to investigate the effects and consequences of NICU procedures. (1,2)

Nociceptive system of very premature infant is functionally immature. Discrimination of noxious and non-noxious stimuli is difficult and descending modulation and inhibitory processes inadequate. (2-6) Also repeated touch, or pain, lead to senzibilization. (4,7)

Reactions to procedural pain related stress may be acute and obvious, behavioral and physiological, such as grimassing, crying, movement, oxygen desaturation, changes in heart rate, respiratory rate, blood pressure. Procedural pain is also associated with feeding difficulties, alterations of sleep-wake states, and apnea. (2,3,8) Pain assesement scales are based on obvious displays of discomfort and stress. (3,9)

Reactions to procedural pain and stress have been investigated by other methods; such as measurement of cerebral blood flow and near infrared spectroscopy of the brain showing alterations of blood supply and oxygenation. (5,10) Also there is significant relationship between pain and oxydative stress. (11) Alterations of cortisol levels were recorded as well. (3,4)

Electroencephalography showed that pain induces diffuse brain activation across the immature brain in very preterm infant. (4,12) Central neuronal activation may be present without visible reactions in very premature infants revealing standardized pain assesment scales as suboptimal tool. (3)

Beside acute reactions on pain and stress due to procedures, consequences on the future life were searched for. The time in NICU, the last trimestar, is the time of rapid brain development, process that may be altered by repeated painful and stressful procedure. (4,13)

Greater exposure to pain related stress is associated with impaired brain develoment and brain microstructure, independent on comorbidities, other insults and injuries. In the studies, exposure to pain was measured as number of skin breaking procedures and intubation from birth to term adjusted for multiple confounding factors. Maturation of white matter and subcortical grey matter is altered, as well as cortical grey matter, resulting in lower cortical thickness and slower head growth. (3,4,13,14)

Neuronal proliferation and cell differentiation, formation of synapses, selective pruning of neuronal processes and synapses happen during the third trimester, the time of exposure to repeated procedures inducing pain related stress in prematurely born infants. (13,15)

Altered brain development may be related to pain related increase in proinflammatory cytokines, oxydative stress, or overstimulation of immature neurons. (3,4,11) Developing brain may be directly influenced by hemodynamic changes at the time of immature autoregulation of cerebral blood flow. (4,5) Also alterations of sleep-wake states may affect developing brain. (4)

At the time of rapid development transitional neuronal structures are particularly vulnerable. Injuries to preoligodendrocytes and sublate zone are especially detrimental. Two proliferative zones subventricular zone and germinative epithelium are also vulnerable, as well as GABAergic neurons and microglia. (13,15) The role of preoligodendrocytes is ensheathement of axons. They are predominant in white matter from 24 to 40 weeks of gestation. Their injury leads to hypomyelination, a designation of periventricular leukomalacia in premature infants, with impaired axonal development affecting neuronal migration with deminished cerebral cortical and thalamus volumes due to trans-synaptic effects (13,15). Subplate zone serves as a waiting compartment for thalamocortical and corticocortical afferents with maximal developmental impact between 24 to 32 weeks of gestation. Injury to subplate has secondary maturational disturbances affecting cerebral cortex and thalamus with volumetric deficit. (15) Procedural pain and stress induce cerebral blood flow and oxygen fluctuations, oxidative stress and inflammatory reactions, that impact preoligodendrocytes and subplate zone. (3,13,15). Also, subplate-glutamate receptors involved in pain transmission are more expressed in early life due to developmental stage (3)

Developing brain is affected with stimulation. Pain induces diffuse brain activation across the brain in very preterm infant. (4) Non-noxious stimuli might as well. (3,4) Possible mechanism of brain injury is that pain and stress lead to high stimulation of immature vulnerable neurons susceptible to overstimulation and excitotoxic damage, especially at the time of early development while thalamocortical connections are waiting in in the subplate zone. (14) Increased neuronal activation of immature developing circuity may be detrimental by altering apoptosis and survival. Repeated noxious nociceptive stimulation may cause rewiring. (13).

As long-term effects of procedural pain and stress were recognized efforts of reduction became an imperative.

REDUCTION OF PAIN AND STRESS

Non-pharmacological measures

Non-nutritive sucking (NNS) promotes comfort and calmness. It is associated with increased oxygenation, improvement in respiratoty and gastrointestinal functions, decreased heart rate and energy expenditure (16) It is effective in reducing pain, especially when combined with sweeteners. (9,17) It was shown to reduce pain of heel lance better than facilitated tucking alone. (16)

Facilitated tucking is a process of gently manually keeping the infant's limb flexed still allowing the infant control over body and some movement. Facilitated

tucking activates proprioceptive, tactile and thermal systems, favors self-soothing behaviour. A containment that still allows some movement sends the central nervous system a continous stream of stimuli that competes with painful stimuli and modulates pain perception, attenuates responses to painful stimuli, and facilitates self-regulation (11,16) Facilitated tucking is developmentally supportive and provides some pain relief. It can be achieved by swadling the infant gently in the blanket. When infant is in the blanket and nest during procedure reduces crying and heart rate changes. Tucking and swadling should be started before the procedure and maintained for some time after. (16)

Skin-to-skin contact or Kangaroo care stimulates tactile and proprioceptive systems and reduces pain. It decreases behavioral and physiological responses on painful procedures and has other benefits for the infant. (11,16) It should be started before and continued after the procedure. (16)

Combination of sweateners and NNS with other non-pharmacological measures attenuates physiological and behavioral responses to painful procedures. Tucking, swadling and skin-to skin are reccomended in junction with sweateners and NNS, topical anaesthetic if indicated, during venipuncture, heel lance, intramuscular and subcutaneous injections, nasogastric or orogastric tube insertion, percutaneous insertion of central cathethers, endotracheal suctioning and screening for retinopathy of prematurity (ROP) (10,17-19) During screening for ROP this combination reduces the responses but does not provide appropriate pain relief with pain scores remaining high. (18)

Other modalities of non-pharmacological measures include sensorial saturation, multi-modal sensory inputs and massage during procedure. Sensorial saturation and massage distract the neonate and provide the stimuli to stop pain transmission to the cerebral cortex. (17) Music, lullaby and mother's voice seem to ease pain responses. (20)

Breast milk is not as effective as sucrose and breastfeeding appears not to be effective in providing pain relief in premature infants. (16)

Neonatal development care includes broad category of proceedings to minimize the effects of NICU stress exposure, such as control of external stimuli, kangaroo and parental involvement, nesting, swadling, prone positioning, and pain management. With higher quality of neonatal developmental care conducted, behavioral outcome is better (21). Neonatal development care does not decrease the pain responses during eye examination for ROP but results in faster recovery (22)

Sweeteners - sucrose and glucose

Sucrose is an established modus for pain and stress reduction of minor procedures. (10,11,23,24,31-33) Optimal dosing, mechanism of action, soothing versus analgesic effects and long term consequences are not completely defined yet. (9,24)

Current reccomendations are for sucrose to be applied through the pacifier or directly to the tongue to ventilated infants 2 minutes prior to procedure. 24% solution is commonly used. Recommended doses depend on the gestational age and severity of procedure: 24 to 26 weeks gestational age 0,1 ml, 27 to 31 0,25, 32 to 36 0,5 ml. (17,24) Recent study revealed that minimal dose of 0,1 ml might be as effective as larger doses suggesting that just exposure to sucrose is relevant, not the amount. (25) Practice of 2 minutes before the stimulus with 4 minutes lasting effect has been challenged by recent data of immediate effect when used with non-nutritive sucking. (26)

Sucrose appears to increase response of endogenous endorphine, possibly dopaminergic and cholinergic pathways, though might augment the anti-nociceptive response. (9,27)

Worse neurodevelopmental scores at term were recorded in infants who had received more than 10 doses per day in the first week of life. (27) Sucrose should be tracked as medication. (9)

Sucrose dampens pain behaviours but does not reduce the cortical pain signal which is an issue for brain vulnerability. (12,14,28) The question remains whether despite generation of electrical activity in the brain of premature infant interpretation of the procedure is other than painful. Sucrose provides more comfort but might not prevent negative effect of pain on neuronal programming. (28,29)

In conjuction with other non-pharmacological measures sucrose provides an additive analgesic effect. (9) Non-nutritive sucking has a synergic and enhanced effect. (17,24) Oral sucrose is used as a first line in all painful procedures, combined with other measures. (17,23) It is not effective for retinopathy of prematurity screening (ROP). (18) Also it is not effective for heel lance (17,23)

Glucose is an alternative to sucrose. Glucose is also effective for brief procedures and can be used as a substitute for sucrose but dose and timing are not established. Currently 10-33% glucose are used at doses 1-2 ml. (9) Most find it uneffective for longer procedures and eye examination for ROP. (9,30)

Topical anesthetics

Eutectic mixture of local anesthetics - EMLA cream may reduce pain for some procedures. It is applied 60 minutes before the procedure and covered with an occlusive bandage. Newer topical anesthetics with shorter onset of action of 30 minutes, but not more effective, are 4% tetracaine gel and 4% liposomal lidocaine cream. Although some NICU use tetracaine gel some find it uneffective in neonates. Methemoglobinemia, especially in premature infants, is accentuated concerns if topical anesthetics are used properly. Transient skin rashes are possibility. Topical anesthetics in combination with sweateners and non-pharmacological measures have found to be effective in venipuncture, percutaneous central cathether insertion, intramuscular or subcutaneous injections and lumbar puncture. They are not effective in reducing pain for heel lancing. (9,17,31)

Before screening for ROP anesthetic eye drops are applied. Mostly used are 1% tetracaine chlorhydrate, 0.5% proparacaine (proxymetacaine), 0.4% oxybuprocaine, equal parts combination of tetracaine chlorhydrate and oxybuprocaine chlorhydrate. No pharmacological side effects are recorded. Topical anesthetics do not ameliorate but marginally decrease pain of the eye examinations. Still, due to futility of other strategies, other than opioids, their use is mandatory in efforts of pain reduction. (17,18,32)

Drugs

Nonopioid analgesic acetaminophen i**s n**ot effective for procedural pain in premature infants. (33) It has not found a place in NICU as a sole agent in preventing and treating acute pain. Use of acetaminophen is promoted in treatment of postoperative pain in combination with opioid drugs which dosage can be decreased. (9) It may be used for mild pain in conjuction with non-pharmacological measures. Overdosage that may cause liver damage is rare in infants but caution is reccomended due to slower clearence. (33).

Nonsteroidal anti-inflammatory agents, indomethacin and ibuprofen, are also not an option. They are associated with complications such as gastrointestinal bleeding, decreased glomerular filtration, pulmonary hypotension and platelet disfunction. Their use in population of premature infants is limited to treatment of patent ductus arteriosus. (9)

Opioids are most effective for treatment of acute pain in premature infants. They provide adequate analghesia but also sedate and attenuate stress responses. (31)

Fentanyl is a widely used opioid analgesic in NICUs. It provides rapid analgesia which makes it appropriate for preventing procedural pain especially in more acute situations such as exigency for intubation. Adventage of fentanyl is minimal sway on haemodynamics, moderate sedation effect and relatively short action. It rapidly crosses the blood-brain barrier, blocks endocrine stress responses and prevents pain-induced responses such as increase in pulmonary resistance. (32,34,35) Hepatic clearence capability increases after 2 weeks after birth. The disandvantages are potential effect on bowel evacuation, especially meconium passage, effect on respiration drive, and chest wall rigidity. (36) Problems are rapid tolerance development and withdrawal symptoms in cumulative doses and prolonged continous infusion. (31,34,35) Higher cumulative dose in premature infants were associated with cerebellar injury and lower cerebellar diameter at term reached. (37) However cumulative doses of fentanyl did not show correlation with 5-year developmental outcomes. (38) Data suggest that in ventilated infants fentanyl provides neuroprotective effect due to protection from pain and stress. (39) Fentanyl is reccomended for prevention of pain of invasive procedures, especially in ventilated and haemodinamically unstable infants. (31)

Fentanyl derivates remifentanil, alfentanil and sulfentanil are in increased usage for prevention of procedural pain due to their shorter-acting feature. Remifentanil is twice as potent and of ultra-short duration of action. It is rapidly cleared by plasma esterases so excretion is independant of liver and renal function, so it is rapidly metabolised and does not accumulate. Alfentanil is less potent, with short duration of action. Alfentanil and sulfentanil are metabolised by liver resulting in increased levels in premature infants after repeated use. They are reccomended for brief invasive procedures. (31,34,40)

Ketamine is effective analgesic, unique for providing deep sedation while maintaining respiratory drive and producing bronchodilatation, also improving hemodynamic function, while mildly increasing heart rate and blood pressure. It does not significantly affect brain blood flow. High doses can however reduce heart rate and blood pressure. Some reccomend usage in haemodynamic unstable infants, such as those with congenital heart diseases and diaphragmal hernia. Still possible neurotoxicity remains concern. (8,9,31) Some NICUs use it for intubation and ROP screening, especially in unstable infants. (17)

Propofol is associated with bradycardia, desaturation and prolonged hypotension, also clearence and neurotoxicity inversely depend on gestational age. (34,35,40) Although appropriate dosing without reaching the threshold of autoregulation is shown to preserve adequate cerebral blood flow. (41)

Morphine is mostly used for chronic pain, especially in ventilated infants, in continous infusion. It is not reccomended for prevention of acute pain in short procedures. (31,40) Methadone, due to long half-life, is not an option for acute procedural pain management. (9,31,34) Garbapentin might be a choice for visceral hyperalgesia, refractory chronic pain and agitation. (42) Usage of dexmedotamine is spreading in the NICUs although sufficient data are lacking. (39) It causes reduction in the cerebral oxygen saturation probably due to local vasoconstriction even when systemic is avoided. Dexmedotamine is used for continuous sedation and analgesia. It has decreased clearence in premature infants. (43)

It should be underlined that sedatives and anxyolitics do not provide analgesia. (44) When used for sedation and relaxation in combination with analgetic measures caution is advised as they can mask signs of pain. A barbiturate phenobarbital used to be widely utilized in NICUs for sedation. It remains a choice for seizure control with levetiracetam taking over. (44) Benzodiazepins such as midazolam and lorazepam are still of sedative usage. Midazolam is resort in refractory seizures. It causes hypotension with decreases in oxygen saturation and cerebral blood flow velocity and therefore might affect developing brain. Midazolam might be associated with adverse neurological outcome in other terms as well, but still frequently prescribed as sedative. (45) Clearence of midazolam increases with age so adjustment of dosage is recommended accordingly. (45) Some authors discourage use of midazolam in infants of less then 34 weeks of gestation. (40)

Cumulative doses of opioids, and sedatives, may cause abstinence syndrom. Clonidine, although further studies are recommended, is used in NICUs as an adjunct or monotherapy treatment of neonatal abstinence syndrom after intrauterine exposure to drugs. (46,47) It is an alpha-2 adrenergic receptor agonist that reduces sympathetic symptoms of withdrawal. It shortens the duration of drug tapering. Current practice of neonatal exposure is slow tapering of addictive drug and introduction of clonidine if it fails. Earlier introduction of clonidine is considered in prolonged opioid infusion. (46) While treating with clonidine potential decrease in heart rate and blood pressure should be monitored, as well as acydosis and hyperkalemia. (47)

Digest

In regard of measures not affecting central nervous reaction to pain, perception of stimuli and comfort are not negligible part of approach to the little patient. Also haemodynamic changes that add to detrimental effect of pain on developing brain might be suppressed by some methods. Therefore use of sucrose, as well as non-pharmacological methods should be supported in the practice. (4,5,15,17,29)

In terms of cumulative pain reducing choice, what seems more invasive and painful procedure might be a better option. As best example heel squeeezing is the most painful part of the procedure when heel lance for blood sampling is performed. Therefore warming the heel and local anesthetics are not useful. Intravenous sampling is proven as less painful and pain provoked can be relieved with sweateners, non-pharmacological and local measures. When multiple daily sampling is expected central cathethers are recommendable. (17)

In respect to concern of opioid side effects, balance with pain and stress side effects should be deliberated. Endotracheal intubation should be performed with adequate analgesia. Appropriate analgesia facilitates intubation and reduces harmful physiological fluctations, and pain. The same stands for placement of central cathethers in ventilated infants prone to haemodynamic unstability. (17)

Eye examinations for ROP demands to be marked since non-pharmacological measures and sweateners as well as topical anaesthetic have not been proven to be useful in preventing pain. Even instalation of mydriatic eyedrops is proven to cause pain. Screening for ROP is the diagnostic procedure that can not be avoided and must be performed according adopted protocols. In ventilated and haemodynamic unstable patients opioids are strongly recommended. In stable patients combination of other measures might be considered in terms of somewhat lessen behavioral responses and solace. Anesthetics eyedrops are obligatory. (8,18,22,37,48-50)

In view of nursing and care processes, impossibility to discriminate non-noxious and noxious stimuli and following sensibilization are not negligible. For example diaper change can provoke blood flow fluctations and adhesive tape removal is proven to cause oxydative stress. Care procedures should be downsided to essentials (2-6)

In concern of senzibilization, clustering of painful procedures ought to be banned in exception of life-threatening circumstances. Two hours pause is advised. (4,7,17)

PRACTICE OF PROCEDURAL PAIN AND STRESS MANAGEMENT IN CROATIA

Data about procedural pain and stress management were collected from four level 3 and one level 4 NICUs. Used pharmacological and nonpharmacological approaches in routine and mandatory procedures in the care of premature infants were recorded. Procedures for which information was collected are intubation

(primary reanimation in the birth room excluded), tracheal suctioning, placement of intravenous routes (peripheral and central), diagnostic blood sample collection (intravenous, heel lance), ophthalmic examination for retinopathy of prematurity (Table 1).

There are no standardized protocols for procedural pain and stress management in any of the high level NICUs encountered. None of the NICUs uses pain assesment scales. None of the NICUs uses developmental care pain management approach for diagnostic and treatment procedures in forms of individual approach to infant, non disturbive approach or parental involvement, e.g. Kangaroo care while performing procedures. Swadling is a part of routine care in most NICUs but special attention is randomly enforced during procedures. Sweateners are utilized in few NICUs, but often not targeted prior to procedures. Drugs are used randomly, often sedatives.

Use of sweateners, non-pharmacological and pharmacological approaches in prevention and treatment of pain is inconsistent between but also within the encountered Croatian NICUs.

Table 1. *Number of Croatian NICU (of 5 encountered) using pharmacological and non-pharmacological pain management during specific medical procedures in years 2018 and 2022*

Year 2018	Year 2022	Drugs		Topical anaesthetics		Sucrose / Glucose		Swadling/ Tucking		Sensorial saturation /massage		Parental involvement	
Elective intubation		R all	1, R 3	/	1	/	/	none	none	none	none	none	none
Tracheal suctioning		none	none	/	/	none	none	none	R 1	none	none	none	none
Percutaneous central routes		R all	1, R 4	none	none	none	R 1	none	none	none	1	none	none
Peripheral venous routes / sampling		none	R 1	none	none	R 1	R 2	none	R 1	none	1	none	none
Heel lance		none	none	/	/	none	none	none	R 1	none	1	none	none
Eye exam for ROP		none	1 after exam	all	all	none	none	none	R 1	none	none	none	none

R = random

CONCLUSION

Preventing, reducing and treating pain and concomitant stress are beholden part of the endevour to preserve and improve life and health of premature infants. The effects of pain and stress on the infant should not be ignored in actions of treatment of what might impose as more important and rather recognized threat on the outcome. Procedures performed in order of better outcome can be detrimental. The extent of pain/stress impact on the outcome of the premature infant is proven and should be adopted as a trajectory of chronic complications of prematurity. As such the attempts of prevention have to be incorpareted in the practice. In search of optimal approach current recomendations have to be granted: reduction of number of procedures, prediction and detection of pain, pain prevention and treatment; in nonpharmacological way when effective. If rational number of interventions is performed gross of medications and sweateners with possible side effects would not be reached.

Overall, awareness of pain and stress in Croatian high levels NICUs exists, but recognition of pain and stress malevolence is still insufficient. Noted progress of pain control is hopeful. Practice of contemporary neonatal medicine has to implement the pain/stress control programme in order to improve the outcome of Croatian NICU patients. We believe that institution of pain management protocols in each NICU, with interexpert agreement, would significantly improve the practice. We propose the pain and stress management for procedures covered in this analysis of Croatian NICUs' consuetud (Table 2).

Table 2. *Proposed procedural pain management for abstracted procedures*

Procedure	*Pain/stress management*
Elective intubation	Drugs[1]
Tracheal suctioning	Sweateners (+ non-nutritive sucking)[2] swadling, facilitated tucking
Percutaneous central venous routes	Sweateners (+ non-nutritive sucking)[2] drugs[1]
Peripheral venous routes/sampling	Sweateners (+ non-nutritive sucking)[2] Swadling / facilitated tucking Topical anaesthetics if MV or HU
Heel lance	Sweateners (+ non-nutritive sucking)[2] Swadling / facilitated tucking or parental involvement[3]
Ophthalmic examination for ROP	Sweateners (+ non-nutritive sucking)[2] Swadling / facilitated tucking or parental involvement[3] Topical anaesthetics Drugs[1] if MV or HU

[1] we suggest fentanyl, preferably remifentanil if available [2]chiefly sucrose, combined with non-nutritive sucking when possible [3]carried out; Kangaroo care or facilitated tucking, depending on the condition of the infant MV = mechanical ventilation HU = haemodynamic unstable

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SAŽETAK

UBLAŽAVANJE UTJECAJA PROCEDURALNE BOLI I STRESA U IZRAZITO NEZRELE NEDONOŠČADI: SADAŠNJA SAZNANJA I HRVATSKA PRAKSA

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Dugo vremena smatralo se da nedonošad nije sposobna osjetiti bol. Izrazito nezrela nedonoščad izložena je brojnim dijagnostičkim i terapijskim intervencijama tijekom boravka u jedinicama intenzivnog liječenja. To se vrijeme u ove skupine nedonoščadi podudara s vremenom brzog razvoja mozga kada su prijelazne neuronske strukture izvanredno osjetljive. Ponavljani bolni i stresni postupci kao neizbježan dio liječenja i skrbi dokazanog su utjecaja na razvoj mozga prijevremeno rođenog djeteta. Priznavanjem dugoročnih učinaka boli i stresa kao i napori da se ti učinci spriječe postaju imperativ neonatalne medicine. Izlažemo pregled nefarmakoloških i farmakoloških metoda kontrole proceduralne boli, njihova djelovanja, poznatih nuspojava i učinkovitosti. Također se osvrćemo na praksu jedinica intenzivnog liječenja trećeg i četvrtog stupnja u Republici Hrvatskoj. Nefarmakološke metode kao što su nenutritivno sisanje, pomognuti utješni položaj odnosno umatanje djeteta, kontakt roditelja i druge metode pokazale su se djelotvornima u ublaživanju boli tijekom mnogih postupaka praćenima blažom boli, a u kombinaciji s lokalnim anesteticima i sladilima i u onih umjerena intenziteta. Nefarmakološke metode utječu na prijenos bolnog podražaja te kao i sladila smanjuju odgovor na bolni podražaj. Među farmacima opioidi su daleko najučinkovitiji tijekom intervencija izrazito bolnog učinka te nuspojave boli i stresa treba uravnotežiti s nuspojavama lijekova. Među procedurama za izdvojiti je oftalmološki pregled probira za retinopatiju nedonoščadi neizbježan postupak stresan za nedonošče već pri samoj primjeni kapi u oko, u kojega su samo opioidi dokazali apsolutnu učinkovitost što svakako treba imati na umu u strojno ventilirane i hemodinamski nestabilne djece. Također treba izdvojiti neučinkovitost kako nefarmakoloških metoda tako i lokalnih anestetika pri uzimanju krvnih uzoraka ubodom u petu. Sveukupno gledano, u hrvatskim jedinicama intenzivnog liječenja novorođenčadi visokog profila svijest o boli u nedonoščadi postoji no priznavanje negativnih učinaka i djelovanje u smislu prevencije, posebice tijekom postupaka blažeg do umjerenog intenziteta još uvijek je relativno slabo. Vjerujemo da bi uvođenje protokola za kontrolu boli u svakoj hrvatskoj neonatološkoj jedinici značajno unaprijedilo praksu te u ovom članku predlažemo taj protokol. Kontrola boli i popratnog stresa obavezan su dio napora za očuvanjem i poboljšanjem života i zdravlja izrazito nezrele nedonoščadi. U traganju za optimalnim metodama tekuće preporuke nužno je sustavno usvajati. U prvom redu redukcija broja procedura, a potom predikcija i detekcija boli te njezina prevencija i liječenje, nefarmakološkim metodama kada su dokazano učinkovite, sustavan su dio suvremene neonatalne prakse u svrhu poboljšanja ishoda ove osjetljive populacije.

Ključne riječi: nedonoščad, novorođenče, bol, liječenje boli, analgezija, retinopatija nedonoščadi