UNIWERSYTET MIKOŁAJA KOPERNIKA W TORUNIU

Collegium Medicum
im. Ludwika Rydygiera w Bydgoszczy

Ludwik Rydygier Collegium Medicum in Bydgoszcz,

Nicolaus Copernicus University in Toruń,

Faculty of Medicine

Interdisciplinary internationally oriented PhD Studies in English

Agnieszka Witulska-Alagöz

PAIN IN NEONATES

DOCTORAL DISSERTATION

PhD Supervisor

Dr hab. n. med Iwona Sadowska-Krawczenko,

PhD in Medicine,

Professor at the Nicolaus Copernicus University in Toruń

Bydgoszcz 2023

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my esteemed supervisor
Prof. Iwona Sadowska-Krawczenko for her invaluable support and assistance
at every stage of the research project and for the mentorship
during the whole course of my PhD degree.

I would like to thank my husband Toygan, my son Artur, my beloved Parents and Friends.
Without their tremendous understanding, patience and encouragement
it would all be impossible.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

BP	-	blood pressure
BIPAP	-	Biphasic Positive Airway Pressure
COVERS	-	Crying, oxygen requirement, vital signs, expression, resting, signaling distress scale
COVID-19	-	Coronavirus Disease 2019
COX-2	-	cyclooxygenase-2
CRIES	-	crying requires increased oxygen administration
DAN	-	Douleur Aigue Nouveau-ne (Newborn Acute Pain)
ECG	-	electrocardiography
EDIN	-	Echelle de Douleur et d'Inconfort du Nouveau-Ne, Neonatal Pain and Discomfort Scale
EEG	-	Electroencephalogram
EMLA	-	Eutectic Mixture of Local Anesthetic
EPIPPAIN study	-	Epidemiology of Procedural Pain in Neonates
FLACC	-	Face, Legs, Activity, Cry and Consolability scale
fMRI	-	functional magnetic resonance imaging
GA	-	gestational age
GW	-	gestational week
HFVI	-	High Frequency Variability Index
HR	-	heart rate
HRV	-	heart rate variability
IASP	-	The International Association for the Study of Pain
INSURE	-	the intubation-surfactant-extubation technique
N	-	number (number of patients in the statistical analysis)
NA	-	not applicable (in the statistical analysis)
N-PASS	-	Neonatal Pain, Agitation and Sedation Scale
NCPAP	-	Nasal Continuous Positive Airway Pressure

NEOPAIN study	-	Neurologic Outcomes and Preemptive Analgesics in Neonates
NFCS	-	Neonatal Facial Coding System scale
NICU	-	Neonatal Intensive Care Unit
NIPE monitor	-	Newborn Infant Parasympathetic Evaluation monitor
NIPE index	-	Newborn Infant Parasympathetic Evaluation index
NIPEm	-	mean NIPE index, to assess prolonged pain and discomfort
NIPEi	-	instantaneous NIPE index, to assess acute nociception
NIRS	-	Near Infrared Spectroscopy
NIPS	-	Neonatal Infant Pain Scale
NMDA	-	N-methyl-D-aspartate
NOPAIN study	-	Neonatal Outcome and Prolonged Analgesia in Neonates
PAT	-	Pain Assessment Tool scale
PIPP	-	Premature Infant Pain Profile scale
PC-SIMV	-	Pressure Controlled Synchronized Intermittent Mandatory Ventilation
PC-PSV	-	Pressure Controlled – Pressure Support Ventilation
RR	-	respiratory rate
SatO2	-	oxygen saturation
SC	-	Skin Conductance
SIMV+VG	-	Volume Guarantee Synchronized Intermittent Mandatory Ventilation

I. INTRODUCTION

The great advance in medicine in last 30 years enabled the dynamic progress in neonatology and in the intensive care of newborns. The Neonatal Intensive Care Unit is a place that provides live-saving medical care for increasing number of patients each year.

With the vast development of medical diagnostic and treatment options the survivability of newborn infants is improving too. As it became possible to rescue even extremely preterm neonates it means for them prolonged hospitalization at the neonatology ward – place of special care with delicacy, compassion and support provided by health professionals but on the other hand unfriendly environment without constant closeness of mother and numerous painful procedures performed daily.

It has been confirmed that despite the vast knowledge and experience still neonates are subjected to noxious events for diagnostic and treatment reasons without sufficient analgesia [121]. The prevention of pain in newborns should be the goal of whole medical team working together to save their lives.

Early and cumulative pain exposure in vulnerable neonates at the critical period of their development has been associated with adverse neurodevelopmental complications [158]. Therefore the great concern about these consequences gives the motivation to use the best, reliable tools to assess pain in newborns accurately and start the optimal and individually tailored treatment followed by regular evaluation providing the best pain management strategy [152].

1. HISTORY OF PAIN IN NEONATES

Until the late 80s of XX century pain in newborns was highly neglected and untreated. Even though it was visible to see baby crying after painful incidents, health providers did not consider that reaction as conscious, only as physiological reflexes. Neonates were thought to be incapable of pain perception because of their immaturity of nervous system and lack of myelinization. Moreover it was generally believed that they would not remember painful experiences too [2]. In result procedures and surgeries normally carried out in adults with provided pain management, in newborn infants were performed without analgesia. What is more anesthesiologists had been aware of complications due to extreme torture-like pain during medical procedures [8, 123]. Clinicians feared of potential negative effects of anesthesia and analgesic drugs that were not accurately studied before in that age as well [202].

The scientific evidence for real pain experience that newborns actually feel were first presented in clinical trials around 30 years ago [7]. Anand et al. assessed the hormonal-metabolic stress responses of neonates undergoing surgical ligation of patent ductus arteriosus. They proved that severe anxiety and pain leading to increased stress-related hormones in unanesthetized infants had great impact on clinical outcomes and was associated with high postoperative mortality [12].

Researchers started exploring underlying mechanisms of pain in neonates, studying its epidemiology in neonatal intensive care setting and various clinical situations of newborn infants, revealing harmful consequences on the brain and further psychomotor development of children in danger of prolonged or repeated noxious stimuli [106]. This significant progress in understanding of neonatal pain led to developing lots of assessment methods and studying on better and safer options for analgesia.

2. EPIDEMIOLOGY

The incidence of neonatal pain is high – much too high. Studies regarding the epidemiology of pain in newborns demonstrate that infants in neonatal intensive care units are subjected to around 16 painful procedures every day (some neonates even up to 62 procedures associated with pain per day) [40]. The most common are heel pricks, venipunctures, insertions of peripheral venous catheters and gastric tube insertions or endo-tracheal suctioning/ aspiration. Researchers managed to conclude with regret that majority of noxious events at NICUs are performed without any form of analgesia [37,83]. The EPIPPAIN study in France showed that around 80% of procedures were carried out without providing proper pain relief in newborns. The prevention of pain in critically ill infants is the ethical obligation of all professional health providers at neonatal departments [24]. Newborns are not just collection of symptoms, they are delicate and sensitive humans suffering from their illnesses, tremendous stress and many painful attacks. They deserve to be treated with empathy.

3. DEFINITION OF PAIN

The International Association for the Study of Pain (IASP) defined pain in 1979 as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” [180]. In 2020 the definition was revised to state that pain is “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” [180]. The change allowed non-verbal, incapable of self-report patients to be assessed with validated pain indicators.

Pain is a perception which depends on the cognition and sensitivity. Pain can be described in the terms of cognitive, emotional and physiological aspects. The nociception is the ability of nerves to detect noxious stimuli and transmit the information about the painful event to the brain for interpretation – it does not require self-report. It describes perfectly the neonatal pain experience [92]. Inability to communicate in newborns does not negate the possibility of their pain perception.

Anatomically, physiologically and biochemically children are able to feel pain already in the early part of intrauterine growth. Current evidence from neuroscientific studies confirm that even fetuses in the first trimester are capable of pain perception [140, 193]. Newborns after birth experience pain in the same way as older patients. Because of the immaturity their sensitivity to pain is higher [132].

Pain is always a personal experience. It is influenced by various biological, psychological and social factors. The personal pain in newborns is associated with stress, clinical situation and previous exposure to painful stimuli.

The subjective and complex nature of pain especially in non-verbal patients makes pain assessment challenging. Care providers must learn to recognize indicators of pain in neonates or use a reliable objective evaluation method to alleviate their unpleasant impressions or provide proper pain relief treatment.

4. TYPES OF PAIN IN NEONATES

Pain can be categorized according to its duration and its source [99]. **Acute procedural pain** is caused by specific noxious event, has an immediate onset and it is self-limited. Diagnostic and therapeutic procedures in neonatal intensive care unit can be the source of an acute pain [9]. **Acute-prolonged pain** is a result of a clear stimulus, with a definable beginning and an expected end point for example in postoperative trauma, on assisted ventilation, suffering from necrotizing enterocolitis or meningitis [10]. **Chronic pain** in newborns is characterized as a pathological state of pain, there is no apparent biological value and it lasts more than three months, longer than normal tissue healing time. Chronic pain in neonates can be observed in patients diagnosed with osteogenesis imperfecta [97].

5. PAINFULL PROCEDURES IN NEONATAL CARE

Neonates are subjected to numerous painful procedure during their hospitalization in intensive care units. They suffer from the excess of necessary diagnostic and therapeutic methods [212]. The procedure is considered to be painful if it invades the integrity of newborn's body causing for example skin breaking or injury, mucosal irritation or injury. Pain is a way of signaling for the body about the tissue damage and the potential danger for health [134].

Diagnostic procedures performed in neonatal intensive care units include heel lancing, venipunctures, arterial punctures, intravenous cannulation, finger sticks, insertions of umbilical catheters involving manipulation of the skin around the umbilical cord and sutures, bladder catheterizations, insertions of central catheters and lumbar punctures. [71]

Potentially painful therapeutic procedures are nasal and tracheal aspirations and suctioning, removal of adhesive sensors or dressings and wounds treatment, gastric tube insertions, tracheal intubations, subcutaneous and intramuscular injections, chest tube placements and drainage, therapeutic hypothermia or even physiotherapy. [23, 176]

Chest drain insertions are perceived to be one of the most painful procedure and heel-prick the last [2].

Pain in neonates can be also related to inflammation and hyperalgesia of injured tissue for example after surgery or localized irritation of skin or mucosa with abrasions and lesions caused by sensors of monitoring devices, adhesive tapes, nasal cannulas, intubation tubes. Clinical states of necrotizing enterocolitis or meningitidis are the source of persistent pain in newborns as well [11].

Hospitalization at the neonatal intensive care unit involves apart from all of these above noxious procedures or diseases causing painful experience, many frequent stressful events for sick newborns. Blood pressure measurement, head ultrasound, electroencephalogram, x-ray, oral aspiration, and even nursing care, weighing and washing routines in the unpleasant environment without mother's presence and support may worsen the general comfort of neonates [40].

Continuous therapies like non-invasive ventilation support with nasal positive pressure or invasive mechanical ventilation by tracheal intubation may be associated with stress, discomfort and pain as well and many of clinicians neglect that fact.

6. EFFECTS OF PAIN IN NEWBORNS

Noxious stimuli in neonates lead to short and long term effects. All of them can result in negative consequences increasing morbidity during hospitalization or causing adverse neurodevelopmental changes diagnosed over next years following the discharge from the neonatology departments.

Direct signs of pain in newborns can be categorized into behavioral, physiological, hormonal or neurophysiological effects [37]. Different factors have impact on their type of expression or intensification: gestational age, illness, medications or the alert state of the patient [20]. **Behavioral signs** of nociception that are possible to observe in infants are: body movements (like limb withdraws) and changes in muscle tension; crying or moaning sounds; hyper-alert state; facial expressions (grimace, brow bulge, squeezed eyes, raised cheeks); decreased quality of sleep [172]. **Physiological signs** of pain in neonates include fluctuations (increase or decrease) of respiration rate, heart rate and heart rate variability (HRV), oxygen saturation, blood pressure [185, 203]. What is more the cortisol level variabilities can be measured in plasma, saliva or urine (**hormonal effects**). Other biochemical changes

including increased release of catecholamines, glucagon, growth hormone, renin, aldosterone and antidiuretic hormone may be observed as well [132]. Furthermore during painful stimuli specific **neurophysiological changes** can be detected in cerebral oxygenation (monitored with Near Infrared Spectroscopy - NIRS), pain-related evoked potentials may be observed in multi-channel EEG or activation of brain pain-sensitive areas are visible in functional magnetic resonance imaging (fMRI) too [88].

Immediate consequences of pain in newborn infants result in irritability, disturbance of sleep and wakefulness state, ventilation-perfusion mismatch, increased gastric acidity and decreased nutrient intake.

Direct signs – short term effects of neonatal pain are the indicators and components of pain assessment scales developed to evaluate newborns and provide proper pain management [164].

Early repetitive pain exposure in neonates is also associated with negative long-term physiological, cognitive and social effects [82, 199, 209]. Newborns routinely experience pain when they are treated in intensive care. Mostly these are premature infants born in the critical period of their development with very high risk of adverse outcomes. They are more vulnerable to stress and noxious stimuli because of their immaturity [29].

Clinicians observe increased sensitivity in neonates born prematurely. It can be the result of lower pain thresholds and the lack of inhibitory controls, because they develop later, closer to the date of planned term birth [135]. What is more long periods of painful events may lead to higher excitability and further to hyperalgesia which is abnormally increased sensitivity to pain [34, 54, 79, 81, 207]. Another likely consequence is allodynia characterized as perception of intense pain after non-noxious stimuli like physical examination or even a change of a diaper [92].

Direct responses to pain like acute increase of heart rate, blood pressure and intracranial pressure may lead to reperfusion injury of central nervous system causing risk of intraventricular hemorrhages and periventricular leukomalacia [29]. Moreover it was confirmed in some studies that repetitive painful experience in newborns lead to more neurodegenerative changes in brain like reduced volume of brain, abnormal white matter microstructure and altered subcortical gray matter and maturation [31, 37, 60].

Possible long-term complications of neonatal pain and stress are behavioral abnormalities and psychosocial problems for example hyperactivity syndrome, separation anxiety or phobias [29, 75]. Other potential adverse neurodevelopmental changes include poor motor performance, attention deficits, learning disorders, altered visual-perceptual ability and impaired cognitive functions [51, 59, 210].

Chronic stress, discomfort, many painful events and maternal separation in newborns in NICUs is additionally related to changes in programming of the hypothalamic-pituitary-adrenal (HPA) axis that is responsible for impaired adaptation to unpleasant surrounding environment and may have impact on brain functioning [81].

All above neurodevelopmental consequences in newborns are as well connected with perinatal risk factors and prematurity itself. The excessive pain exposure amplify the possible negative outcomes [125, 206, 211].

II. ASSESSMENT OF PAIN IN NEONATES

One of the principal goals of perinatal and neonatal care is to decrease infant mortality and to improve neurodevelopmental outcomes in newborns that are born prematurely and/or treated in intensive care units [16]. The great concern of all neonatologists, pediatricians, anesthesiologists, nurses, midwifes and other members of neonatological care about all detrimental effects of pain, motivate to search for the best, reliable tools to asses pain in newborns accurately and start the optimal treatment [6].

Pain assessment tools are underutilized as many studies and questionnaires among staff members showed [2]. Mostly it is caused by lack of the knowledge and neglecting the necessity of pain management in patients. In addition the excess of daily duties in neonatal intensive care units and the lack of time caused by general overload aggravates the inadequate and insufficient pain prevention and management in newborns.

Neonates are unable to communicate verbally, but this not negate they are incapable of feeling pain. Because of the absence of self-report pain evaluation in newborns is challenging and in many clinical situations like during ventilation especially in preterm infants unclear to detect [7]. To evaluate pain in neonates and to prevent its adverse short term and long term effects in children in preverbal stage of development pain scales and pain monitor are available. The decision of which assessment method to choose depends mainly on the age, clinical state and type of experienced pain [26]. Accurate evaluation of patients enables further individualized treatment.

1. PAIN SCALES

A large number of scales to assess pain and discomfort has been created since the topic of pain sensitivity of newborns emerged [76]. Even though around 65. of them have been validated in many clinical trials still it is not possible to standardize worldwide the usage of one gold-standard scale for every neonate [139]. Scales can be behavioral or multidimensional, univariable or multivariable [15, 145]. They are constructed for specific types of pain or targeted to different clinical applicability of patients like after surgery, during sedation

or in ventilated patients [150]. Age of the baby is one of parameter to consider while choosing the best suitable assessment scale. In the table nr 1 presented below the most popular pain scales are listed.

Table 1. Pain assessment scales in newborns [76].

TYPE OF PAIN/ CLINICAL SETTING	SCALE	AGE
Acute pain	Behavioral Indicators of Infant Pain	24-32 GW
	Adapted COMFORT	28-37 GW
	Faceless Acute Neonatal Pain Scale	30-35 GW
	PASPI Pain Assessment Scale for Preterm Infants	27-36 GW
	ABC Pain Scale	32-41 GW
	APN/DAN Acute Pain in Newborns	25-41 GW
	COVERS Neonatal Pain Scale [87]	23 GW – 2 moths
	CRIES Scale	32 GW – 1 month
	Harrison	28-41 GW
	Infant Body Coding System	25-41 GW
	NIAPAS Neonatal Acute Pain Assessment Scale	23-42 GW
	NIPS Neonatal Infant Pain Scale	27 GW – 7 months
	N-PASS Neonatal Pain, Agitation and Sedation Scale [97]	23-30 GW
	PIPP Premature Infant Pain Profile	32-40 GW
	PIPP-R Premature Infants Pain Profile Revised	From 26 GW
	Scale for Use in Newborns	24 GW – 7 months
	COMFORT-Behavior Scale	35 GW – 4 years
	NFCS Neonatal Facial Coding System	29 GW – 18 months
	Observational Visual Analog Scale	35 GW – 4 years
	Alder Hey Triage Pain Score	0 – 16 years
	EVENDOL behavioral pain scale [26]	0 – 7 years
	FLACC Face, Legs, Activity, Cry and Consolability	1 day – 7 years
	Pain Observational Scale for Young Children	0 – 4 years
	Royal College of Emergency Medicine Composite Pain Scale	0 – 16 years
	Touch Visual Pain Scale	0 – 13 years
	UWCH University of Wisconsin Children's Hospital Pain Scale	0 – 16 years
Prolonged pain	EDIN Scale	26 – 36 GW
	Modified Postoperative Comfort Score	29 – 32 GW
	COMFORT Neo	24 – 43 GW
	Modified EDIN	31 – 38 GW
	Faces Pain Scale – Revised	25 GW – 3 months

	N-PASS Neonatal, Pain, Agitation and Sedation Scale	23 – 30 GW
	Pain Assessment in Neonates	26 – 47 GW
	PAT Pain Assessment Tool [98]	23 GW – 6 months
	Swedish ALPS-Neo	23 – 41 GW
	COMFORT	24 GW – 18 years
	COMFORT-Behavior Scale	35 GW – 4 years
	NFCS Neonatal Facial Coding System	29 GW – 18 moths
	Shortened NFCS	35 GW – 18 months
	EVENDOL Scale	0 – 7 years
Postoperative pain	CRIES Scale	32 GW – 1 month
	Objective Pain Scale	32 – 60 GW
	PAT Pain Assessment Tool	23 GW – 6 moths
	PIPP Premature Infant Pain Profile	32 – 40 GW
	CHIPPS Children's and Infants' Postoperative Pain Scale	35 GW – 5 years
	Multidimensional Assessment of Pain Scale	36 GW – 31 months
	NFCS Neonatal Facial Coding System	29 GW – 18 months
	Liverpool Infant Distress Scale	Term newborns
	Cardiac Analgesic Assessment Scale	0 – 16 years
	FLACC Face, Legs, Activity, Cry and Consolability	1 day – 7 years
	NAPI Nursing Assessment of Pain Intensity	0 – 36 months
	POCIS Pain Observation Scale for Young Children	0 – 4 years
	POPS Postoperative Pain Score	0 – 36 months
	RIPS Riley Infant Pain Scale	0 – 36 months
Ventilation	Modified Postoperative Comfort Scale	29 – 32 GW
	Nepean Neonatal Intensive Care Unit Pain Assessment Tool	25 0 36 GW
	Bernese Pain Scale for Neonates [171]	27 – 41 GW
	NFCS Neonatal Facial Coding System	29 GW – 18 months
	Shortened NFCS	35 GW - 18 months
	Hartwig	0 – 10 months
Sedation	COMFORT Neo	24 – 43 GW
	Modified COMFORT	23 – 54 GW
	N-PASS Neonatal Pain, Agitation and Sedation Scale	23 – 30 GW
	COMFORT	24 GW – 18 years
	Hartwig	0 – 10 months
	Ramsay Sedation Scale	0 – 19 years

The most commonly used scales at neonatal intensive care units are: the EDIN scale, the Bernese Pain Scale for Neonates, the COMFORT scale, the CRIES scale, the N-PASS scale, the PAT scale, the PIPP and PIPP Revised scales, the NFCS scale, the EVENDOL scale and the FLACC scale [170].

Unfortunately pain scales have a lot of limitations that impede to use them routinely to assess newborns. Well-trained nurses, midwifes and clinicians had questioned their reliability to evaluate different types of pain and to distinguish nociception and discomfort. What is more pain scales require prolonged observation for scoring patients. The evaluation by scales is also believed to be subjective, the result may differ among observers. Furthermore pain assessment is intermittent and there is a high risk of omission of painful events. On the other hand pain scales for evaluation of newborns are generally underutilized among neonatological team members [178].

Behavioral and physiological indicators of pain are scored in the pain scales. In the state of prolonged pain some of neonates become passive with very few or even no body movements and expressions of their face which can lead to incorrect biased pain assessment results [141, 186]. So called immobility syndrome is defined as facial contraction with blank expression and paucity of spontaneous movement of extremities. Physiologically decreased heart and respiratory rate as well as lower oxygen saturation can be observed as well. These could be the visible mark of conservation of energy and have impact on pain assessment using some specific scales [6, 103]. In other cases of patients suffering from prolonged pain exposure, agitation syndrome can be detected, which is characterized too by facial contraction like in immobility state, but with hypertonia and excessive body movements especially during the interactions with medical personnel [55].

Additionally premature infants with relatively immature nervous systems or neonates with neurological impairment may not manifest their painful experience as termly born babies especially with facial expressions [183, 187, 200, 201]. Newborns less than 33 gestational age are less reliable able to display their reactions to noxious stimuli and it is difficult to interpret their behavioral responses in pain scales [74, 80].

Further investigation of pain assessment tools is needed to improve patients' clinical care and long-term outcomes.

2. PAIN MONITORS

The accuracy of pain assessment is pivotal to improve pain management in neonates [42]. Current efforts and many ongoing studies introduce the use of neuroimaging or neurophysiologic techniques that measure brain activity and monitors evaluating different body responses or physiological parameters to painful stimuli to present visually pain experience in newborns [136, 137]. These tools can measure heart rate variability, skin conductance, cortical neuronal activity or the hemodynamic activity over the somatosensory cortex during different pain experience.

The Newborn Infant Parasympathetic Evaluation pain monitor (NIPE) is the instrumental method to asses pain in neonates with heart rate variability (HRV) [197]. It enables objective and continuous assessment of pain and discomfort by analyzing the parasympathetic component of the autonomic nervous system in newborn babies. Several studies are in progress to assess its clinical reliability and validity in various clinical situations.

NIRS (Near infrared spectroscopy) can be useful for detecting noxious cortical activation resulting from painful events in neonates. It presents pain-associated increases in hemoglobin concentration in the contralateral somatosensory cortex [135]. This technique requires trained staff to conduct and interpret the results. However it is a non-invasive method of pain monitoring and its reliability and validity for pain evaluation in newborns has been studied in several clinical trials so far [90, 94, 167].

Pain monitoring with **electroencephalography (EEG)** assesses cortical neuronal activity [105]. Noxious-evoked individual baseline sensitivity and variability in brain activity is observed as event-related changes of EEG. The activation of cortical neurons and networks can indicate pain in newborns. It is an objective method to quantify infant's nociceptive activity of brain after acute procedural pain [48,67, 89, 108].

Skin Conductance is related to palm and sole sweating and it reflects the increased sympathetic nervous system activity [133]. Panful stimuli results in inducing activity of sweat glands on the palms and soles. The measurement of skin conductivity in these areas is an objective method of pain and discomfort evaluation [108, 128, 143]. The skin conductance monitor may be valuable for the assessment of analgosedation as well [194].

Functional magnetic resonance imagining (fMRI) presents cerebral hemodynamic responses to noxious stimulation with the change of brain activity. It visualizes localized noxious-evoked reactions in the functional brain regions considered to be the part of nociceptive system. The results can be compared with the pain association test map created on the basis of meta-analytic database of fMRI images. What is more the amplitudes of responses may reflect brain maturation [22].

Recently **artificial intelligence (AI) tools** have been studied to recognize and evaluate pain reactions in neonates by recording and analyzing dynamic facial expressions as pain indicators [216]. Accurate pain assessment with AI technology could provide continuous objective evaluation in the neonatal intensive care units [44, 169].

It is still unclear which of these monitoring techniques studied for pain assessment in newborns has the strongest reliability and could be recommended as the objective evaluation for acute, prolonged or chronic pain instead of pain scales that have their limitations in everyday use in NICUs.

III. PAIN MANAGEMENT

Despite the technological advances in pain monitoring and periodic updates of guidelines in pain management strategies, general failure for adequate analgesia during painful procedures is still noticeable. The morbidity of patients hospitalized in neonatal intensive care units is increased which is related to numerous invasive and complicated life-saving diagnostic and therapeutic methods applied to vulnerable infants experiencing pain in critical period of their development. Therefore it is recommended to revise the knowledge according to evidence based up-to-date guidelines to improve the quality of medical care of patients in NICUs [115].

1. PREVENTION OF PAIN

Undoubtedly very high frequency of painful diagnostic and therapeutic procedures performed in neonatology is noted in recent years. The concern about the detrimental consequences of repeated pain experience promoted the tendency to prevent pain which is clearly observed among clinicians. First and foremost limitation of noxious procedures is advised [127]. Careful and reasonable decisions regardless ordering potentially painful methods are paramount. Whenever it is clinically assumed to be adequate non-invasive monitoring is recommended [50]. Instead of blood sampling by puncturing heel or vena, for example the transcutaneous bilirubinmeter in diagnosis of jaundice or the usage of others ways of monitoring like pulse oximetry, near infrared spectroscopy (NIRS) or transcutaneous CO2 detector is recommended. Another method of prevention is clustering of painful procedures, performing them without disturbance of daily routine of the baby and its resting/sleeping time.

Blood sampling by heel-pricks is very frequent painful diagnostic procedure in the intensive care units [144]. Collected blood is used for gas analysis, neonatal screening tests for metabolic diseases or biochemical evaluation for example of electrolytes, bilirubin and glucose. Heel-pricks performed with needle puncture are less painful than via automatic manual lancets [25, 78].

2. NON-PHARMACOLOGICAL METHODS

At the neonatal intensive care unit which can be a hostile environment for critically ill newborns special background conditions are advised to improve their well-being. First of all excessive background acoustic and visual stimuli ought to be limited; soft-colored blankets over incubators, decreased sounds of monitoring alarms or muted cellphones of staff and visitors are one of the examples of recommended interventions [131]. Providing sufficient amount of time for rest and sleep, preventing from excessive sleep deprivation is very important as well [39].

Apart from environmental modifications several pain management approaches of proven lack of adverse effects are available [84]. Procedural pain of mild to moderate severity caused by heel lancing, venipuncture or intermuscular injection can be decreased by the usage of so called non-pharmacological pain-reduction methods [47]. These include: non-nutritive sucking, kangaroo care/ skin-to-skin contact, breastfeeding, sweet solutions administered orally and behavioral methods to increase the comfort and lower the stress level of neonates like specific positioning, delicate handling, swaddling or facilitated tucking [37, 68, 95].

Breastfeeding and breast milk feeding have been proven to reduce discomfort and pain in neonates especially for late preterm and term newborns. Maternal contact and closeness, smell of the mother and sucking allow to alleviate nociception in patients [116, 205].

On the other hand non-nutritive sucking has calming and pain reducing effects as well. Oral stimulation through sucking a pacifier or finger can improve pain reactivity mainly for full-term neonates [30].

Skin-to-skin contact was at the beginning a method to keep newborns warm, to support their body temperature regulation as an alternative to incubator for preterm infants. It had been observed then that close contact between mother and child provided consolability and shortened the time of crying after procedural pain [32, 49, 102, 104].

Kangaroo mother care is mainly recommended after birth to help the adaptation process but it is also useful for providing warmth, decreasing stress, comforting, managing procedural pain and to encourage bonding, but it can have impact on lowering the intensity of procedural pain for example during vaccination [38, 85, 168]. Additionally maternal speech can significantly reduce level of stress in the NICU [65].

Parents of a child treated in the intensive care unit are under tremendous stress about their daughter's or son's life [114]. They observe their infant being subjected to many painful procedures and professional health providers in neonatology departments should involve them in the aspect of patient's pain care [189]. Informing about child's state and regular communication with parents are particularly advised. Parental participation in patient's caregiving activities is not only beneficial for the newborn in pain but also to reduce psychologic distress of parents [69].

Facilitated tucking is another non-pharmacological intervention to reduce pain in newborns by placing hand on the head and limbs of a patient using gentle pressure to comfort them [47, 91]. Other option is to swaddle the baby with hand-shaped pillow to lower their stress and enable proper positioning or nesting in the incubator.

Sweet solutions of glucose or sucrose are the most common and well-known non-pharmacological pain relief methods [33, 113]. Many studies verified administration of sweet solutions to be useful in analgesia of mild pain in newborns by increasing endogenous endorphins. Other studied mechanisms of pain relieving with sucrose or glucose are the stimulation of endogenous opioid, cholinergic, dopaminergic and serotonergic pathways [136]. They are simple to use and easily available. However some of researchers suggest careful recommendations of repetitive sucrose or glucose doses because it can be associated with negative long-term neurodevelopmental adverse effects. Safety of different range of doses is still unsure, studies continue in this topic [184].

Massage therapy also has demonstrated effectiveness in trials for decreasing pain-related reactions. With gentle effleurage, light petrissage and mild compressions the comfort of newborns in stress may be increased [52, 66].

In some countries acupuncture is used for pain relief too by stimulation of endorphin system [77, 130].

A few reports from studies of music therapy and its positive effects to alleviate stress in neonatal intensive care units are also available [13, 47, 138].

All above interventions are more effective if they are combined [177, 204]. For example non-nutritive sucking with orally administered sweet glucose or with skin-to-skin contact were confirmed to be more beneficial than applying each of these methods alone [33, 122, 151].

Non-pharmacological pain management method have many benefits and minor drawback, which promotes them to be recommended for general use in newborns [27].

3. PHARMACOLOGICAL ANALGESIA

The great progress in medicine has enabled carrying out many studies on the pharmacokinetics, pharmacodynamics and efficacy of drugs used for analgesia in newborns, nevertheless there is still not enough data regarding safe and optimal treatment – especially for preterm neonates [62, 84, 188]. Doubts remain about the effective dosage or the possible short-term and long-term negative adverse effects of the drugs recommended for pain relief in infants [58]. The tendency of increasing awareness of neonatal pain lead to improved management of pain in neonatal intensive care units but many studies have shown that many procedures are performed without sufficient analgesia. Physiological stress and late detrimental neurodevelopmental consequences of pain in neonates can be more dangerous than analgesia side effects. Clinicians and other members of neonatological team ought to revise current pain management guidelines to provide evidence-based safest treatment options for their vulnerable patients.

Local anesthetics are useful for many procedures in NICUs. Regional anesthesia with lidocaine infiltration that inhibits axonal transmission by blocking Na+ channels can serve for minor surgeries such as inguinal hernia repair; procedures like chest tube insertion.

Topical anesthetics for example the EMLA cream (a combination of lidocaine and prilocaine) are effective for reducing pain associated with heel lancing, vena puncturing or for the lumbar puncture [117, 185]. Topical creams in preterm newborns who have thinner epidermis and high dermal permeability, should be carefully administered due to the risk of methemoglobinemia [140].

Paracetamol (acetaminophen) has been widely studied in the populations of neonates. It is recommended for management of mild or moderate pain in conjunction with other pain relief non-pharmacological methods [146]. Paracetamol inhibits the COX-2 enzymes. Its is frequently used in neonates, administered mainly intravenously [72]. Oral and rectal routes may be problematic in patients of this age [86]. The usage of paracetamol for pain relief in newborns decreased the opioid overuse and it is advised in the opioid-sparing treatment

approach [214]. Nevertheless available data from studies strongly suggest that paracetamol is not adequate to reduce acute procedural pain [3].

Non-steroidal anti-inflammatory drugs like ibuprofen are not advised for newborns for analgesia. They are approved as one of the treatment method to close patent ductus arteriosus. Apart from their pain relieving and anti-inflammatory effects, their benefits do not overcome the concern about adverse sequels including renal disfunction or impaired platelet adhesiveness.

Opioids are commonly used analgesic drugs for moderate to severe pain in newborns. They are also sedatives. Morphine is the most frequent opioid in neonates of different gestational age. It can be used as a continuous infusion for prolonged pain or intermittently to reduce the acute pain. It has slow onset of analgesia – around 5 min, peak effect is observed at 15 minutes after administration. Possible adverse effects of morphine include hypotension, prolonged need for ventilation and full parenteral feeding, higher incidence of mortality [192]. A few studies have raised suspicion of negative complications in brain like intraventricular hemorrhages or periventricular leukomalacia. In the NEOPAIN (Neurologic Outcomes and Preemptive Analgesics in Neonates) study on the other hand continuous morphine infusion was not proved to increase the risk of negative neurologic outcomes in ventilated preterm babies [9, 61, 85].

Fentanyl is a fast acting purse synthetic opioid and it provides rapid analgesia with minimal hemodynamic sequels for example for intubation procedure. Side effects of fentanyl administration observed in infants are chest wall rigidity, bradycardia and tolerance after prolonged therapy, but on the other hand it is associated with reduced complications of decreased gastrointestinal motility or urinary retention in comparison with morphine. Intravenous administration via syringe pump lasting minimum 3 min. is advised to avoid chest wall rigidity [112, 136, 217].

Other short-acting opioids: remifentanil and sulfentanil are also in use for neonatal pain reduction especially if quick recovery is anticipated [5].

With the advances in neonatology and years of clinical observations routine use of opioids for prolonged treatment is not recommended [28].

Dexmedetomidine is a highly selective alpha-2-adrenergic receptor agonist and can be used for newborns for analgesia, anxiolysis and sedation. The clinical experience of usage of dexmedetomidine for neonates increases. It is believed to be a potential substitution to opioids [175]. Possible side-effects include bradycardia and hypotension although in the studies carried out so far showed they were clinically insignificant and did not required additional pharmacological intervention [147]. Dexmedetomidine is an alternative method of analgesia during therapeutic hypothermia in hypoxic ischemic encephalopathy instead of opioids [136]. In addition, possible neuroprotective effects on immature brain of neonates were described in preclinical trials. Dexmedetomidine may be effective in analgesia for mechanically ventilated newborns as well [46].

Clonidine is an alpha-2-agonist like dexmedetomidine. Available data on its usage in term and preterm newborns are limited. It may provide analgesia, induce sedation and ameliorate anxiety. The benefits and possible harms of clonidine for pain treatment are being studied [166, 173].

Gabapentin is a gamma-aminobutyric acid (GABA) analog. It blocks the release of excitatory neurotransmitters in the central nervous system which cause pain. The usage of gabapentin for neonates is gaining attention of more clinicians. Gabapentin reduces chronic irritability and feeding intolerance in patients with visceral hyperalgesia due to gastrointestinal morbidities [179, 213].

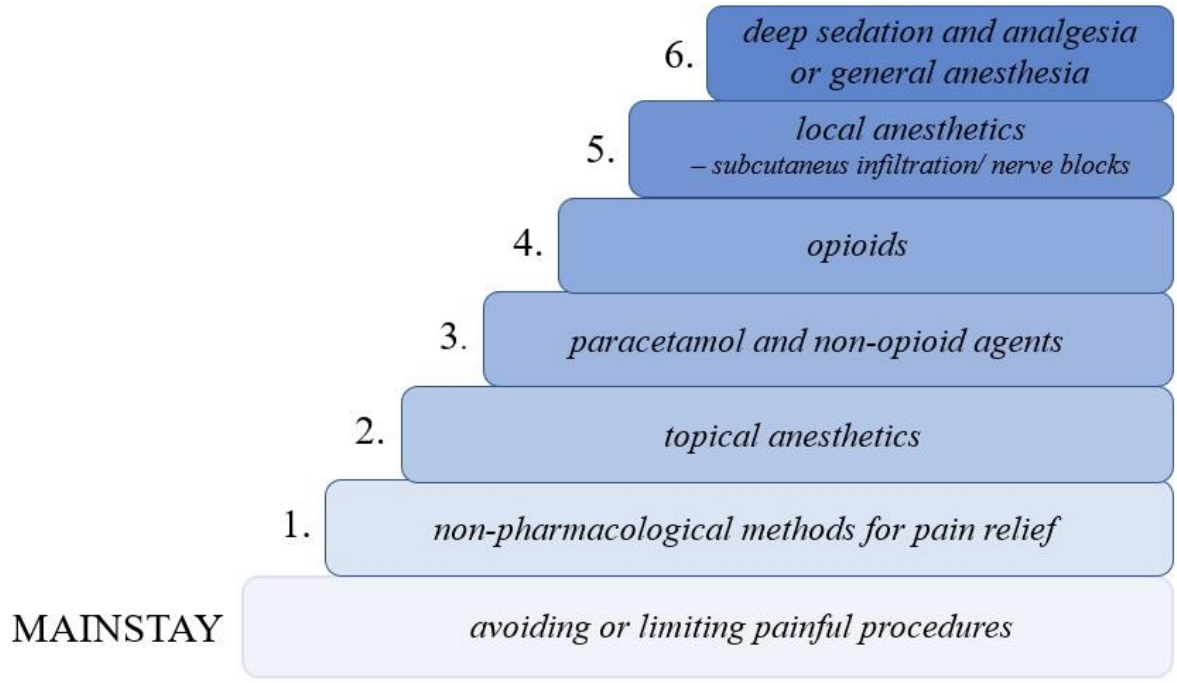
Benzodiazepines in neonatal intensive care are recommended for sedation and muscle relaxation. They work as adjuvants to analgesic drugs. These sedatives may also cause significant physiologic perturbances related to depression of respiratory and/or circulatory systems (hypotension) which can lead to adverse neurologic outcomes. Other possible complication is myoclonic jerking. Midazolam is the most commonly used short-acting benzodiazepine that produces anxiolysis, sedation, amnesia and muscle relaxation for newborns. It is frequently administered in premedication for endotracheal intubation [18]. Concerns regarding its use in neonates resulting in adverse short and long-term effect have also been described in trials (the NOPAIN study). It can cause respiratory depression, hypotension, bradycardia and it may decrease of cerebral blood flow in preterm newborns [84].

Ketamine is the analgesic drug that provides also amnesia and sedation. It is an N-methyl-D-aspartate (NMDA) antagonist with rapid onset of action around 1-2 min. and quite short time of pain relieving effect up to 15-30 min. Ketamine is advised for hypotensive and unstable neonates since it does not affect cerebral blood flow. Some of studies suggested even its neuroprotective effect reducing neuronal cell death. Ketamine on the other hand may increase heart rate, blood pressure and respiratory rate. The recommendations regardless ketamine use for neonatal analgesia are becoming more popular among clinicians [190].

Melatonin is a neurohormone with potential benefits of its analgesic, antioxidant and anti-inflammatory functions. Promising results were assumed in studies to control pain in ventilated preterm newborns [39].

To summarize available data on pain management methods in newborns, a reasonable, depending on the clinical situation and severity of pain (related to the specific procedure), stepwise approach is recommended together with regular pain assessment [84]. Figure 1. presents the analgesic ladder strategy for pain relief in neonates.

Figure 1. The analgesic ladder strategy for pain relief in neonates.



To start optimal treatment of pain in neonates the proper accurate pain assessment is crucial. Searching for a behavioral scale to be announced as a gold standard in pain evaluation in newborns has failed up to now. Therefore more studies of pain diagnostic methods are necessary to obtain the best tool, useful for many clinical situations and reliable to assess newborns in different gestational age.

IV. AIMS OF THE STUDY

The overall aim of the study was to establish the utility of the NIPE pain monitor in different clinical situations at the department of neonatology and to assess its reliability to monitor pain in newborns.

The objective of the first phase of the study of pain was to assess and compare different methods of pain evaluation in preterm neonates experiencing acute prolonged pain: the Newborn Infant Parasympathetic Evaluation (NIPE) index; the Neonatal Pain, Agitation and Sedation Scale (N-PASS); the Premature Infants Pain Profile (PIPP) and the Neonatal Pain and Discomfort Scale (EDIN).

The objective of the second sub-study was to evaluate of the level of pain in neonates caused by an acute procedural noxious event and to assess their sensitivity to pain depending on gestational age using the Newborn Infant Parasympathetic Evaluation (NIPE) index.

V. MATERIAL AND METHODS

The study of pain in neonates was conducted at the tertiary care Neonatal Intensive Care Unit of the Department of Neonatology, Dr Jan Biziel's University Hospital nr 2 in Bydgoszcz in Poland.

It was carried out between February 2019 and December 2022. The duration of the study was prolonged than originally presumed due to the outbreak of the COVID-19 pandemic in 2019.

1. STUDY DESIGN

The study of pain in neonates consisted of two experimental components. The topics of them were:

1. "Clinical reliability and utility of the NIPE pain monitor in neonates. Comparison of the Newborn Infant Parasympathetic Evaluation (NIPE) index; the Neonatal Pain, Agitation and Sedation Scale (N-PASS); the Premature Infants Pain Profile (PIPP) and the Neonatal Pain and Discomfort Scale (EDIN) for assessment of acute prolonged pain in preterm neonates."

2. "Evaluation of the level of pain in neonates caused by acute procedural noxious event with assessment of their pain sensitivity depending on gestational age using the Newborn Infant Parasympathetic Evaluation (NIPE) index."

Both of these researches were combined and performed simultaneously as some of patients included for the first assessment were as well evaluated in terms of the second topic when they experienced acute procedural pain and met the inclusion criteria of the second additionally.

Both phases of the trial were designed as prospective observational studies.

2. SAMPLE

Inclusion criteria for **the first experimental group** were: preterm neonates on assisted ventilation: invasive or non-invasive. These children were presumed to suffer from acute prolonged pain that from the definition is the pain where there is a specified stimulus like ventilation, with clearly delineable beginning and an expected end point. Term newborns, children with neurological or cardiac congenital anomalies, patients diagnosed with arrhythmias or circulatory failure requiring infusion of vasopressive drugs or fluid resuscitation, babies with severe encephalopathy were excluded from the trial.

In **the second experimental group** neonates born at different gestational age subjected to acute procedural pain were enrolled for the assessment. Exclusion criteria were as follows: neurological or cardiac congenital anomalies, arrythmia, circulatory failure requiring infusion of vasopressive drugs or fluid resuscitation and severe encephalopathy.

The control group consisted of healthy newborns not subjected to any noxious stimuli during their observation.

3. PROTOCOL

Neonates were assessed using NIPE pain monitor and three pain scales: N-PASS, PIPP and EDIN, all of them previously validated and widely used clinically in neonatal intensive care units all over the world.

The NIPE – Newborn Infant Parasympathetic Evaluation Index - monitor (MDoloris, France) is a device used to measure the intensity of pain and level of analgesia in newborns. It is a non-invasive method that analyze heart rate variability representing the parasympathetic/ sympathetic tone balance of autonomous nervous system. Specifically newborn's HRV of high frequencies over 0,15 Hz reflects parasympathetic activity which is suitable for monitoring pain. The NIPE monitor presents values from 0 – 100. The more pain/discomfort the child experience, the lower is the result on the display. The index decreases with the intensity of noxious event. The NIPEm index represents the mean value over 20 min. of observation and it is advised to be used for assessment of prolonged or chronic pain and discomfort of patients. The NIPEi – instantaneous value – is derived from an algorithm calculating the short term HRV up to 3 min. It reflects the real time level of pain, therefore can be applied for assessment of acute nociception. NIPE values less than 50 indicate either pain, discomfort or stress [73, 208, 215]. The monitor has to be connected to the cardiac monitor. The Philips IntelliVue MP30 device was used for every observation in the study. Heart rate, respiratory rate and oxygen saturation of evaluated children were recorded from its displayed values too.

Every patient's observation during the study last at least 20 min. The NIPEm scores were recorded at 0, 5, 10, 15 and 20 min., and afterwards median result from these five records was calculated (the NIPEm median result). If the patient was subjected to additional procedural painful stimulus monitoring was prolonged at least for 20 min. after the noxious event. At the end of observation the "end NIPEm" index was recorded. Other values noted during evaluation were: the initial NIPEm, the minimal NIPEi, the maximal NIPEi. Newborns monitored to control their pain sensitivity had one more value calculated – the decrease of NIPE index (%) to examine what was the difference between the NIPEm median result and the minimal NIPEi.

The N-PASS scale is one of the most commonly used tool for pain assessment in neonates born prematurely or on term, especially for prolonged pain [107]. Five parameters are evaluated as follows: crying/irritability, behavior/state, facial expression, extremity tone and vital signs: heart rate, respiratory rate, blood pressure and oxygen saturation. These five criteria are scored from -2 to +2. Calculated result higher that +3 indicates pain. Low results less than -3 mean sedation of patient [142]. Table nr 2. presents N-PASS scale used for patients assessment.

Table 2. N-PASS (Neonatal Pain, Agitation and Sedation) Scale [57]

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	Appropriate crying Not irritable	Irritable or crying at intervals Consolable	High-pitched or silent, continuous cry Inconsolable
Behavioral state	No arousal to any stimuli, No spontaneous movement	Arouses minimally to stimuli Little spontaneous movement	Appropriate for gestational age	Restless, squirming Awakens frequently	Arching, kicking Constantly awake or arouses minimally/ no movement (not sedated)
Facial Expressions	Mouth is lax No expression	Minimal expression with stimuli	Relaxed Appropriate	Any pain expression intermittent	Any pain expression continual
Extremity tone	No grasp reflex Flaccid tone	Weak grasp reflex Weak muscle tone	Relaxed hands and feet Normal tone	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, SaO2	No variability with stimuli Hypoventilation or apnea	<10% variability from baseline with stimuli	Within baseline or normal for gestational age	↑ 10-20% from baseline SaO2 76-85% with stimulation quick ↑	↑ >20% from baseline SatO2 <=75% with stimulation slow ↑

HR: heart rate, RR: Respiratory rate, BP: Blood pressure, SaO2: oxygen saturation

The PIPP scale is the second well-adapted in neonatal intensive care units tool for acute and postoperative pain assessment in patients [181]. Apart from that it was several times used for evaluating ventilated patients with prolonged pain [155]. Components of gestational age, behavioral state, brow bulge, eye squeeze, nasolabial furrow and change of physiological parameters like heart rate, oxygen saturation are being scored in the PIPP scale. The maximum result is 21, and minimum is 0 points. The score >= 6 indicates moderate pain. If the score is higher than 12 it stands for severe pain [1]. The table nr 3. presents the PIPP scale used for pain evaluation.

Table 3. PIPP (Premature Infant Pain Profile) Scale [181].

		0	**1**	**2**	**3**
Gestational age		>=36 weeks	32-35 weeks, 6 days	28-31 weeks, 6 days	< 28 weeks
15 seconds Infant observation	**Behavioral state**	Active/awake Eyes open Facial movements	Quiet/awake Eyes open No facial movements	Active/sleep Eyes closed Facial movements	Quiet/sleep Eyes closed No facial movements
30 seconds Infant observation	**Heart rate**	0-4 beats/min. increase	5-14 beats/min. increase	15-24 beats/min. increase	>= 25 beats/min. increase
	Oxygen saturation	0%-2,4% decrease	2,5%-4,9% decrease	5,0%-7,4% decrease	7,5% decrease or more
	Brow bulge	< 9% of time	10%-39% of time	40%-69% of time	>70% of time
	Eye squeeze	<9% of time	10%-39% of time	40%-69% of time	>70% of time
	Nasolabial furrow	<9% of time	10%-39% of time	40%-69% of time	>70% of time

The EDIN scale evaluates five behavioral indicators of prolonged pain in neonates: facial activity, body movements, quality of sleep, quality of contact with nurses and consolability. Every single parameter is given from 0 to 3 points. Final result higher or equal 5 demonstrate pain in assessed patient. The EDIN assessment tool is validated and appropriate for monitoring prolonged pain like during ventilation in neonates of different gestational age [55, 157]. The EDIN scale is presented below at the Table nr 4.

Table 4. EDIN (Echelle de Douleur et d'Inconfort du Nouveau-Ne, Neonatal Pain and Discomfort) Scale [55].

Indicator	Description
Facial activity	0. Relaxed facial activity 1. Transient grimaces with frowning, lip purse and chin quiver or tautness 2. Frequent grimaces, lasting grimaces 3. Permanent grimaces resembling crying or blank face
Body movements	0. Relaxed body movements 1. Transient agitation, often quiet 2. Frequent agitation but can be calmed down 3. Permanent agitation with contraction of fingers and toes and hypertonia of limbs or infrequent, slow movements and prostration
Quality of sleep	0. Falls asleep easily 1. Falls asleep with difficulty 2. Frequent, spontaneous arousals, independent of nursing, restless sleep 3. Sleepless
Quality of contact with nurses	0. Smiles, attentive to voice 1. Transient apprehension during interactions with nurses 2. Difficulty communicating with nurses. Cries in response to minor stimulation 3. Refuses to communicate with nurses. No interpersonal rapport. Moans without stimulation
Consolability	0. Quiet, total relaxation 1. Calms down quickly in response to stroking or voice, or with sucking 2. Calms down with difficulty 3. Disconsolate. Sucks desperately

Patients in experimental group in discomfort caused by acute prolonged pain were ventilated invasively being intubated on Pressure Controlled Synchronized Intermittent Mandatory Ventilation (PC-SIMV), Pressure Controlled-Pressure Support Ventilation and Volume Guarantee Synchronized Intermittent Mandatory Ventilation modes; or ventilated non-invasively with Nasal Continuous Positive Airway Pressure (NCPAP) or Biphasic Positive Airway Pressure (BIPAP) modes.

Newborns assessed during acute painful stimuli experienced heel lancing, airway suctioning, vena puncturing or change of the dressing of injuries skin around external nostrils. None of these noxious procedures were performed especially for the study, patient were evaluated only when they had to be subjected to them because of their clinical state or the necessity of blood sample collection for laboratory tests.

During the observation only one patient had morphine administered for analgesia. Unfortunately no other specific pharmacological or non-pharmacological methods of pain relief were used for the patients while evaluation, but after the assessment every neonate was evaluated by the lead clinician for the need of individually tailored pain management.

Newborns were tested during day shifts – between 9:00 and 14:00, so as not to disturb them during their daily routines and resting times. While monitoring three disposable ECG electrodes were attached/ glued (with gel on them) to their skin on the child's chest and later they were removed using special delicate StickOff spray (Chiesi) to avoid additional discomfort and stress.

4. ETHICS

The study of pain was conducted after obtaining approval by local Ethical Committee (KB 265/2019; KB 694/2019). The approvals were prolonged due to the outbreak of the COVID-19 pandemic in 2019.

Informed consents from patients' parents/legal guardians were procured prior to enrollment of newborns.

5. STATISTICAL ANALYSIS

Descriptive statistics were presented in categories of mean, standard deviation, median, minimum and maximum for continuous variables; count and percent for categorical variables. Pearson's Chi-squared test or Fisher's exact test was performed to compare categorical variables between groups, Wilcoxon rank sum test to compare continuous variables between

two groups (e.g. experimental vs. control group) and Kruskal-Wallis rank sum test to compare continuous variables between more than two groups.

Correlation analysis was performed to assess the relationship between all four continuous pain rating scales (N-PASS, PIPP, EDIN and NIPE). Spearman rank-based (non-parametric) correlation coefficient, S test statistic and corresponding p-value for all pairs of pain rating scales are presented.

Additionally, to show the relationship between the behavioral scales and the NIPE system, scatter plots with smoothed conditional means curve with 95% confidence intervals are presented. Due to points overlapping (caused by discreteness of pain rating results), a small amount of random variation (jitter) was added to the location of each point.

Diagnostic performance agreement between behavioral rating scales and the NIPE results (all categorized as pain vs. no pain) was assessed in contingency tables analysis. Cohen's kappa coefficient of reliability with 95% confidence intervals and percentage accuracy were calculated.

The relationship between continuous variables such as gestational age at birth and NIPE score, scatter plots are presented and to show the relationship between categorical variables such as ventilation type and NIPE score, descriptive statistics (count and percent) along with Wilcoxon and Kruskal-Wallis rank sum tests p-values were evaluated.

Linear regression analysis was performed to assess the influence of various factors (continuous and categorical) on the NIPE score (the NIPEm score for patients with prolonged and/or procedural source of pain; the minimum NIPEi, the NIPEm 20 minutes after painful procedure and the percentage decrease of NIPE index for patients with procedural source of pain). Beta coefficients with 95% confidence intervals along with corresponding p-values for univariate linear models were calculated.

All analyses were performed using R statistical software, version 4.2.1, developed by The R Foundation for Statistical Computing.

VI. RESULTS

1. PATIENTS' CHARACTERISTICS

40 patients were assessed in the study (21 male neonates and 19 female neonates): 25 patients were included in the experimental group of ventilated preterm newborns, 15 patients were assessed while experiencing acute procedural pain and the control group consisted of 10 patients in comfort and without any source of pain. Newborns' general characteristics have been presented in the Table nr 5.

Table 5. Patients' characteristics the experimental vs. the control group.

Patient's characteristics, experimental vs. control group	**N**	**Overall, N = 40[1]**	**Experimental group: painful procedure, N = 30[1]**	**Control group: no painful procedure, N = 10[1]**	**p-value[2]**
Gender	40				>0.999
Male		21 (52.5%)	16 (53.3%)	5 (50.0%)	
Female		19 (47.5%)	14 (46.7%)	5 (50.0%)	
Gestational age at birth [weeks]	40				<0.001
Mean (SD)		32.8 (5.1)	30.9 (4.3)	38.5 (1.6)	
Median (Range)		31.3 (24.1, 40.0)	29.7 (24.1, 40.0)	39.2 (34.9, 40.0)	
Weight [g]	40				<0.001
Mean (SD)		2,086 (948)	1,757 (850)	3,073 (350)	
Median (Range)		1,780 (955, 3,830)	1,396 (955, 3,830)	3,065 (2,320, 3,480)	
Day of life when pain was assessed	40				0.225
Mean (SD)		11.4 (17.5)	13.8 (19.7)	4.2 (1.5)	
Median (Range)		4.5 (1.0, 98.0)	8.0 (1.0, 98.0)	4.0 (2.0, 8.0)	
Had procedural pain	40	15 (37.5%)	15 (50.0%)	0 (0.0%)	0.006
Had prolonged pain	40	25 (62.5%)	25 (83.3%)	0 (0.0%)	<0.001

[1]n (%)

[2]Fisher's exact test; Wilcoxon rank sum test

There is no statistically significant difference in gender between experimental and control group (p-value in Fisher's test > 0.999). There is statistically significant difference in gestational age at birth between experimental and control group (p-value in Wilcoxon test < 0.001). There is statistically significant difference in weight between experimental and control group (p-value in Wilcoxon test < 0.001). There is no statistically significant difference in day of life when pain was assessed between experimental and control group (p-value in Wilcoxon test = 0.225).

Table nr 6 presents characteristics of patients in different experimental groups, depending on the source of their pain: acute prolonged or procedural or prolonged and procedural and their NIPE m results and the control group experiencing no pain.

Table 6. Patients' characteristics and the NIPE results, comparison of groups with no source of pain vs. only procedural vs. only prolonged vs procedural and prolonged.

Patient's characteristics and NIPE results, comparison of groups with various sources of pain	**N**	**Overall, N = 40[1]**	**no source of pain, N = 10[1]**	**only procedural, N = 5[1]**	**only prolonged, N = 15[1]**	**procedural and prolonged, N = 10[1]**	**p-value[2]**
Gender	40						0.134
Male		21 (52.5%)	5 (50.0%)	5 (100.0%)	6 (40.0%)	5 (50.0%)	
Female		19 (47.5%)	5 (50.0%)	0 (0.0%)	9 (60.0%)	5 (50.0%)	
Gestational age at birth [weeks]	40						<0.001
Mean (SD)		32.8 (5.1)	38.5 (1.6)	38.3 (1.3)	29.2 (2.6)	29.7 (3.4)	
Median (Range)		31.3 (24.1, 40.0)	39.2 (34.9, 40.0)	38.7 (36.7, 40.0)	28.9 (24.1, 34.9)	29.5 (24.3, 36.4)	
Weight [g]	40						<0.001
Mean (SD)		2,086 (948)	3,073 (350)	3,354 (350)	1,416 (426)	1,470 (538)	
Median (Range)		1,780 (955, 3,830)	3,065 (2,320, 3,480)	3,350 (2,850, 3,830)	1,296 (955, 2,260)	1,376 (970, 2,830)	
Day of life when pain assessed	40						0.131
Mean (SD)		11.4 (17.5)	4.2 (1.5)	3.6 (2.5)	17.5 (25.3)	13.5 (12.9)	
Median (Range)		4.5 (1.0, 98.0)	4.0 (2.0, 8.0)	3.0 (2.0, 8.0)	11.0 (1.0, 98.0)	8.5 (2.0, 36.0)	
NIPEm	40						<0.001
Mean (SD)		52.3 (7.8)	60.7 (2.1)	57.4 (9.4)	48.1 (5.9)	47.7 (4.2)	
Median (Range)		50.5 (41.0, 67.0)	61.0 (58.0, 65.0)	62.0 (45.0, 67.0)	46.0 (41.0, 59.0)	48.0 (41.0, 53.0)	

Table 6. Patients' characteristics and the NIPE results, comparison of groups with no source of pain vs. only procedural vs. only prolonged vs procedural and prolonged.

Patient's characteristics and NIPE results, comparison of groups with various sources of pain	N	Overall, N = 40[1]	no source of pain, N = 10[1]	only procedural, N = 5[1]	only prolonged, N = 15[1]	procedural and prolonged, N = 10[1]	p-value[2]
NIPEm cat	40						<0.001
no pain		20 (50.0%)	10 (100.0%)	3 (60.0%)	4 (26.7%)	3 (30.0%)	
pain		20 (50.0%)	0 (0.0%)	2 (40.0%)	11 (73.3%)	7 (70.0%)	
NIPEm initial	40						0.238
Mean (SD)		49.8 (11.0)	53.7 (10.4)	56.6 (12.8)	46.7 (11.5)	47.2 (8.8)	
Median (Range)		50.0 (25.0, 78.0)	52.0 (37.0, 78.0)	65.0 (37.0, 66.0)	45.0 (25.0, 66.0)	48.5 (36.0, 60.0)	
NIPEm end	40						<0.001
Mean (SD)		53.1 (7.6)	60.7 (2.1)	60.8 (10.0)	48.7 (4.3)	48.3 (4.3)	
Median (Range)		52.5 (41.0, 74.0)	61.0 (58.0, 65.0)	61.0 (46.0, 74.0)	49.0 (41.0, 55.0)	48.5 (41.0, 54.0)	
NIPEi minimum	40						<0.001
Mean (SD)		40.2 (11.2)	53.8 (4.3)	48.6 (9.6)	36.0 (4.4)	28.8 (5.6)	
Median (Range)		39.0 (22.0, 59.0)	55.5 (47.0, 58.0)	52.0 (37.0, 59.0)	37.0 (25.0, 40.0)	28.5 (22.0, 42.0)	
NIPEi maximum	40						<0.001
Mean (SD)		55.7 (9.4)	64.9 (3.6)	63.2 (11.4)	50.1 (7.2)	51.1 (5.3)	
Median (Range)		55.0 (36.0, 74.0)	63.0 (61.0, 72.0)	67.0 (44.0, 74.0)	47.0 (36.0, 63.0)	52.5 (44.0, 58.0)	

[1]n (%)

[2]Fisher's exact test; Kruskal-Wallis rank sum test

Table nr 7 presents characteristics of ventilated patients born prematurely assessed for acute prolonged pain.

In the experimental group assessed for acute prolonged pain 14 female newborns and 11 male neonates were evaluated. The mean gestational age at birth of infants in experimental group of ventilated preterm neonates was 29.4 weeks (range 24.1 - 36.4 weeks) and mean weight was 1437.7g (range 955g – 2830g). 4 neonates (16%) were ventilated invasively (intubated on PC-PSV, PC-SIMV or SIMV+VG mode) and 21 newborns (84%) on ventilation support with non-invasive method (NCPAP - 18 patients, BIPAP – 3 patients). The median day of life when patients were evaluated was 15.9 day (range 1.0 – 98.0).

The result of the NIPEm median result – counted from 5 results of patient's observation during at least 20 minutes range from 41.0 to 59.0 (mean result among all includes 25 patients was 48.0. According to the recommendations of the MDoloris Medical Systems Company that produced the monitor, results less than 50 mean than patient is in discomfort and feels pain. 18/25 patients in this experimental group had results lower than 50 (72%). The mean end NIPEm result displayed and recorded after 20min. of continuous observation was 48,6 (range 41.0 – 55.0).

The mean minimal NIPEi index showing the actual short-termly assessed discomfort was 33.1 (range 22.0 – 42.0).

Table 7. Patients' characteristics and the NIPE results, group with prolonged pain.

Patient's characteristics and NIPE results, group with prolonged pain	**N**	**N = 25[1]**
Gender	25	
Male		11 (44.0%)
Female		14 (56.0%)
Gestational age at birth [weeks]	25	
Mean (SD)		29.4 (2.9)
Median (Range)		29.0 (24.1, 36.4)
Weight [g]	25	
Mean (SD)		1,437.7 (463.6)
Median (Range)		1,339.0 (955.0, 2,830.0)
Day of life when pain assessed	25	
Mean (SD)		15.9 (21.0)
Median (Range)		9.0 (1.0, 98.0)
Ventilation method	25	
BIPAP Wilamed		3 (12.0%)
NCPAP		14 (56.0%)
NCPAP Wilamed		4 (16.0%)
PC-PSV		1 (4.0%)
PC-SIMV		1 (4.0%)
SIMV+VG		2 (8.0%)
Ventilation type	25	
Invasive		4 (16.0%)
non-invasive		21 (84.0%)
NIPEm score: continuous	25	
Mean (SD)		48.0 (5.2)
Median (Range)		48.0 (41.0, 59.0)

Table 7. Patients' characteristics and the NIPE results, group with prolonged pain.

Patient's characteristics and NIPE results, group with prolonged pain	**N**	**N = 25[1]**
NIPEm score: pain vs. no pain	25	
no pain		7 (28.0%)
Pain		18 (72.0%)
initial NIPEm	25	
Mean (SD)		46.9 (10.3)
Median (Range)		48.0 (25.0, 66.0)
end NIPEm	25	
Mean (SD)		48.6 (4.2)
Median (Range)		49.0 (41.0, 55.0)
min NIPEi	25	
Mean (SD)		33.1 (6.0)
Median (Range)		36.0 (22.0, 42.0)
max NIPEi	25	
Mean (SD)		50.5 (6.4)
Median (Range)		49.0 (36.0, 63.0)

[1]n (%)

Table nr 8 presents characteristics of patients experiencing procedural pain and their NIPE results.

In the experimental group assessed for acute procedural pain 5 female newborns and 10 male neonates were evaluated. The mean gestational age at birth of infants in this experimental group was 32.6 weeks (range 24.3 – 40.0 weeks) and mean weight was 2097.8g (range 970.0g – 3830.0g). 8 newborns experienced heel lancing as the painful procedure resulting in acute pain (53.3%), 2 patients had vena puncturing performed (13.3%), 4 patients had suffered from airway suctioning (26.7%) and 1 patient during observation had external nostrils' injured skin cleaned (6.7%). The mean day of life when patients were evaluated was 10.2 day (range 2.0 – 36.0).

The result of the NIPEm mean result – counted from 5 results of patient's observation during at least 20 minutes range from 41.0 to 67.0 (mean result among all included 15 patients was 50.9). 6/15 patients in this experimental group had NIPEm results lower than 50. The mean end NIPEm result displayed and recorded after 20min. after painful procedure was 52.5 (range 41.0 – 74.0).

The mean minimal NIPEi index recorded withing 3 min after painful procedure was 35.4 (range 22.0 – 59.0).

Table 8. Patients' characteristics and the NIPEm results, group with procedural pain.

Patient's characteristics and NIPE results, group with procedural pain	**N**	**N = 15[1]**
Gender	15	
Male		10 (66.7%)
Female		5 (33.3%)
Gestational age at birth [weeks]	15	
Mean (SD)		32.6 (5.1)
Median (Range)		31.4 (24.3, 40.0)
Weight [g]	15	
Mean (SD)		2,097.8 (1,032.6)
Median (Range)		1,490.0 (970.0, 3,830.0)
Day of life when pain assessed	15	
Mean (SD)		10.2 (11.5)
Median (Range)		6.0 (2.0, 36.0)
Type of procedural pain	15	
heel lancing		8 (53.3%)
vena puncturing		2 (13.3%)
Suction		4 (26.7%)
cleaning of injuried skin around external nostrils		1 (6.7%)
NIPEm score: continuous	15	
Mean (SD)		50.9 (7.7)
Median (Range)		48.0 (41.0, 67.0)
NIPEm score: pain vs. no pain	15	
no pain		6 (40.0%)
Pain		9 (60.0%)
initial NIPEm	15	
Mean (SD)		50.3 (10.8)
Median (Range)		50.0 (36.0, 66.0)

Table 8. Patients' characteristics and the NIPEm results, group with procedural pain.

Patient's characteristics and NIPE results, group with procedural pain	**N**	**N = 15[1]**
end NIPEm	15	
Mean (SD)		52.5 (8.8)
Median (Range)		51.0 (41.0, 74.0)
min NIPEi	15	
Mean (SD)		35.4 (11.8)
Median (Range)		30.0 (22.0, 59.0)
max NIPEi	15	
Mean (SD)		55.1 (9.5)
Median (Range)		54.0 (44.0, 74.0)
Decrease in NIPE score [%]	15	
Mean (SD)		31.6 (15.1)
Median (Range)		36.2 (10.6, 49.1)

[1]n (%)

2. RESULTS OF PAIN EVALUATION WITH PAIN SCALES

Table 9. The N-PASS score, patients with prolonged pain.

N-PASS score	N	N = 40[1]
N-PASS score: continuous	25	
Mean (SD)		3.4 (2.0)
Median (Range)		4.0 (0.0, 6.0)
N-PASS score: pain vs. no pain	25	
no pain		8 (32.0%)
Pain		17 (68.0%)
N-PASS score: no pain/moderate pain/severe pain	25	
no pain		8 (32.0%)
moderate pain		17 (68.0%)
severe pain		0 (0.0%)

[1]n (%)

According to the N-PASS pain score, 17 patients (68%) with prolonged source of pain actually were feeling pain and it was moderate pain. The mean N-PASS score was 3.4. One patient on morphine was assessed with the N-PASS pain scale with the result -6, which was interpreted as no pain (patient was sedated).

Table 10. The PIPP score, patients with prolonged pain.

PIPP score	N	N = 40[1]
PIPP score: continuous	25	
Mean (SD)		7.5 (3.1)
Median (Range)		8.0 (2.0, 14.0)
PIPP score: pain vs. no pain	25	
no pain		6 (24.0%)
Pain		19 (76.0%)
PIPP score: no pain/moderate pain/severe pain	25	
no pain		6 (24.0%)
moderate pain		17 (68.0%)
severe pain		2 (8.0%)

[1]n (%)

According to the PIPP pain score, 19 patients (76%) with prolonged source of pain actually were feeling pain. 17 of them were experiencing moderate pain and 2 of them severe pain.

Table 11. The EDIN score, patients with prolonged pain.

EDIN score	N	N = 40[1]
EDIN score: continuous	25	
Mean (SD)		5.0 (2.4)
Median (Range)		5.0 (0.0, 10.0)
EDIN score: pain vs. no pain	25	
no pain		8 (32.0%)
Pain		17 (68.0%)

[1]n (%)

According to the EDIN pain score, 17 patients (68%) with prolonged source of pain actually were feeling pain.

3. NIPEm RESULTS – IN THE EXPERIMENTAL GROUP AND THE CONTROL GROUP

Table 12. The NIPEm score, the experimental vs. the control group.

NIPEm score	N	Overall, N = 40[1]	Experimental group: painful procedure, N = 30[1]	Control group: no painful procedure, N = 10[1]	p-value[2]
NIPEm score: continuous	40				<0.001
Mean (SD)		52.3 (7.8)	49.5 (6.9)	60.7 (2.1)	
Median (Range)		50.5 (41.0, 67.0)	48.0 (41.0, 67.0)	61.0 (58.0, 65.0)	
NIPEm score: pain vs. no pain	40				<0.001
no pain		20 (50.0%)	10 (33.3%)	10 (100.0%)	
pain		20 (50.0%)	20 (66.7%)	0 (0.0%)	

[1]n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test

The NIPEm score was significantly lower in the experimental group (with any source of pain) than in the control group (p-value in Wilcoxon rank sum test < 0.001).

According to the NIPEm pain score, 20 out of 30 patients (66.7%) from the experimental group and 0 out of 10 patients (0%) from the control group actually were feeling pain.

Significantly more patients were in pain (according to the categorical NIPEm score) in the experimental group than in the control group (p-value in Pearson's Chi-squared test < 0.001).

4. ANALYSIS OF THE CORRELATION BETWEEN PAIN ASSESSMENT SCALES AND NIPEm RESULTS

Table 13. Correlation between the N-PASS, the PIPP, the EDIN and the NIPEm scores.

	NPASS	PIPP	EDIN	NIPEm
NPASS	1.000	0.748	0.904	-0.821
PIPP	0.748	1.000	0.716	-0.597
EDIN	0.904	0.716	1.000	-0.851
NIPEm	-0.821	-0.597	-0.851	1.000

Pain scale 1	Pain scale 2	Spearman correlation	S statistic	p value
N-PASS	PIPP	0.748	655.7	<0.001
N-PASS	EDIN	0.904	250.7	<0.001
N-PASS	NIPEm	-0.821	4,734.3	<0.001
PIPP	EDIN	0.716	738.6	<0.001
PIPP	NIPEm	-0.597	4,153.1	0.002
EDIN	NIPEm	-0.851	4,812.8	<0.001

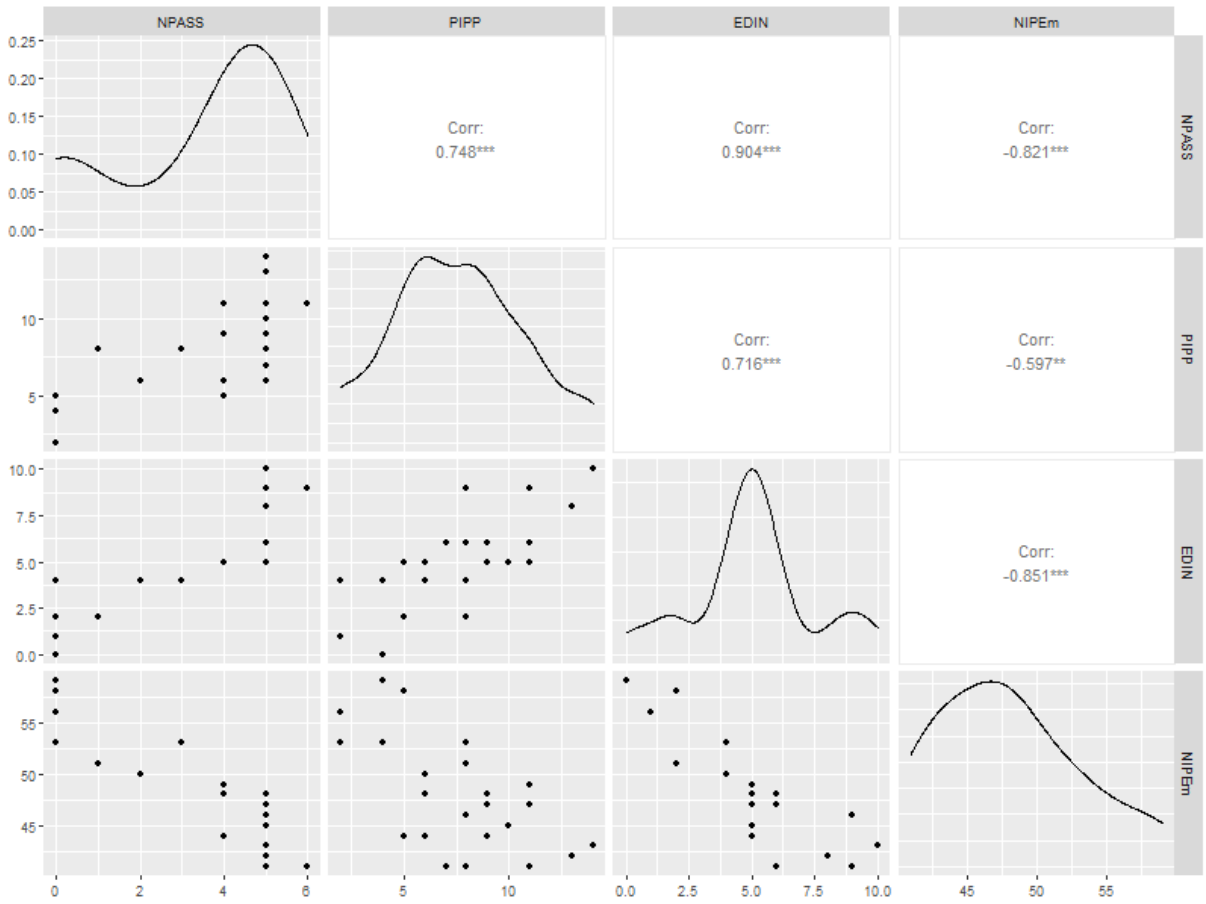


Figure 2. Correlation between the N-PASS, the PIPP, the EDIN and the NIPEm scores

There is very strong and highly significant positive Spearman correlation between the N-PASS, the PIPP and the EDIN score (p values <0,001.)

There is very strong and highly significant negative Spearman correlation between the N-PASS score and the NIPEm score (p value <0,001), the PIPP score and the NIPEm score (p value 0,002), the EDIN score and the NIPEm score (p value <0,001).

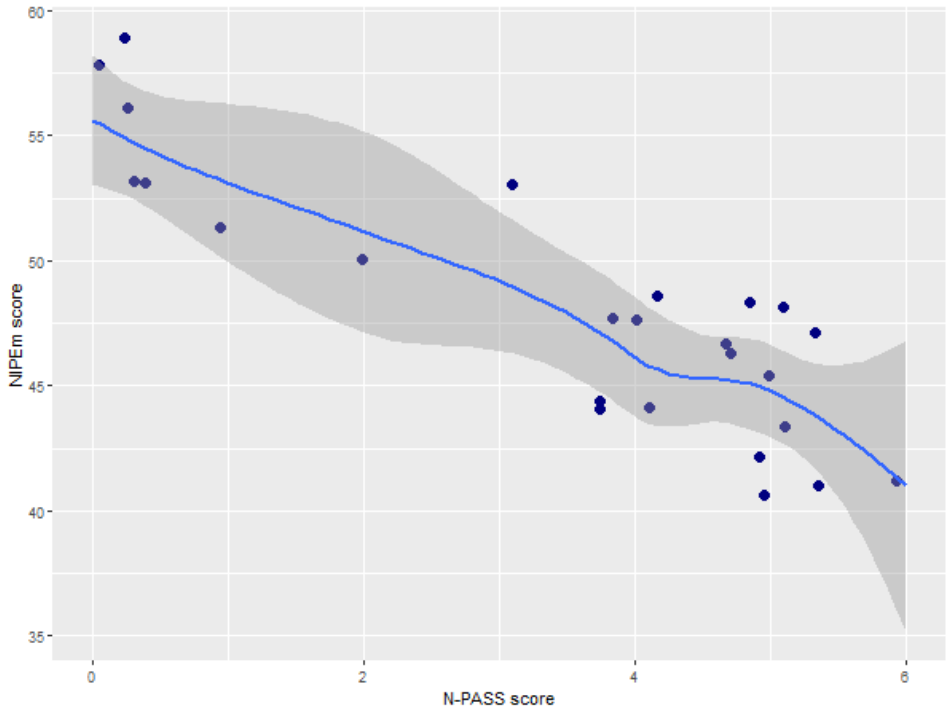


Figure 3. The NIPEm score vs. the N-PASS score, points jittered, smoothed conditional means curve with confidence intervals.

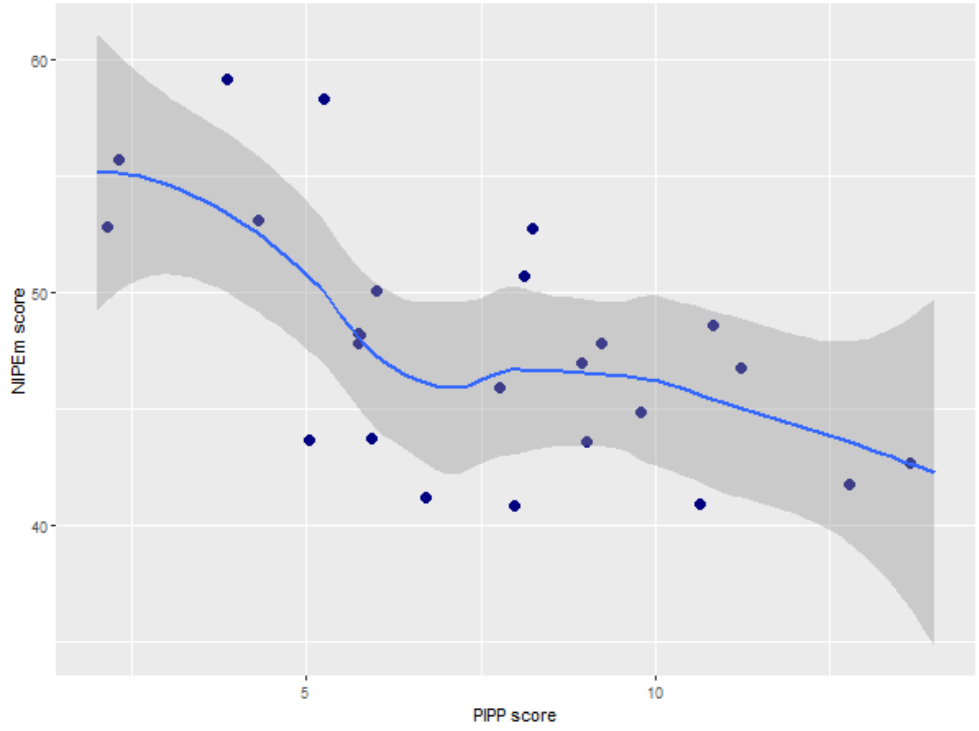


Figure 4. The NIPEm score vs. the PIPP score, points jittered, smoothed conditional means curve with confidence intervals.

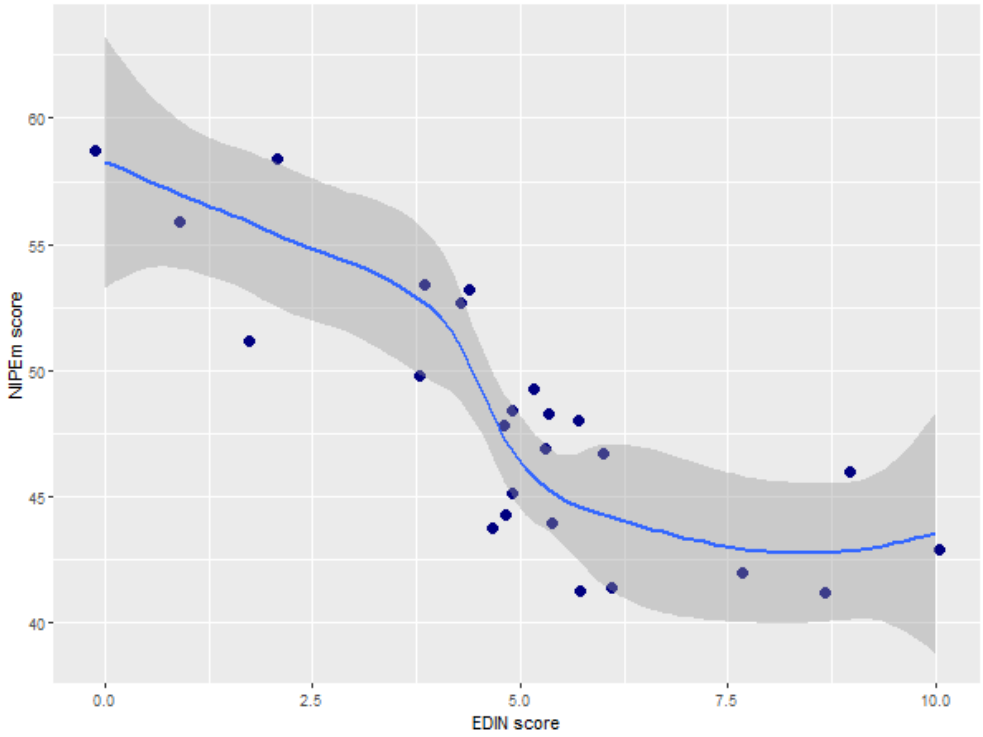


Figure 5. The NIPEm score vs. the EDIN score, points jittered, smoothed conditional means curve with confidence intervals.

5. ANALYSIS OF THE DIAGNOSTIC PERFORMANCE AGREEMENT

Table 14. The N-PASS, the PIPP, the EDIN and the NIPEm scores – agreement between categorical rating.

	NIPEm score		
	no pain	**pain**	**Total**
N-PASS score			
no pain	7 (28.0%)	1 (4.0%)	8 (32.0%)
pain	0 (0.0%)	17 (68.0%)	17 (68.0%)
Total	7 (28.0%)	18 (72.0%)	25 (100.0%)

	NIPEm score		
	no pain	**pain**	**Total**
PIPP score			
no pain	5 (20.0%)	1 (4.0%)	6 (24.0%)
pain	2 (8.0%)	17 (68.0%)	19 (76.0%)
Total	7 (28.0%)	18 (72.0%)	25 (100.0%)

	NIPEm score		
	no pain	**pain**	**Total**
EDIN score			
no pain	7 (28.0%)	1 (4.0%)	8 (32.0%)
pain	0 (0.0%)	17 (68.0%)	17 (68.0%)
Total	7 (28.0%)	18 (72.0%)	25 (100.0%)

Table 15. Accuracy between pain scales and the NIPEm index.

Behavioral rating score	NIPEm index score	Cohen kappa coefficient with CI	Accuracy
N-PASS score	NIPEm score	0.905 (0.723, 1)	96%
PIPP score	NIPEm score	0.689 (0.364, 1)	88%
EDIN score	NIPEm score	0.905 (0.723, 1)	96%

There is very high agreement between the N-PASS score and the NIPEm score (Cohen's kappa = 0.905, accuracy = 96%), the PIPP score and the NIPEm score (Cohen's kappa = 0.689, accuracy = 88%), the EDIN score and the NIPEm score (Cohen's kappa = 0.905, accuracy = 96%).

6. NIPEm RESULTS VS. PATIENTS CHARACTERISTICS ANALYSIS

Figure nr 5, 6 and 7 present the NIPEm results vs. gestational age at birth, vs. weight and vs. day of life when patients were evaluated.

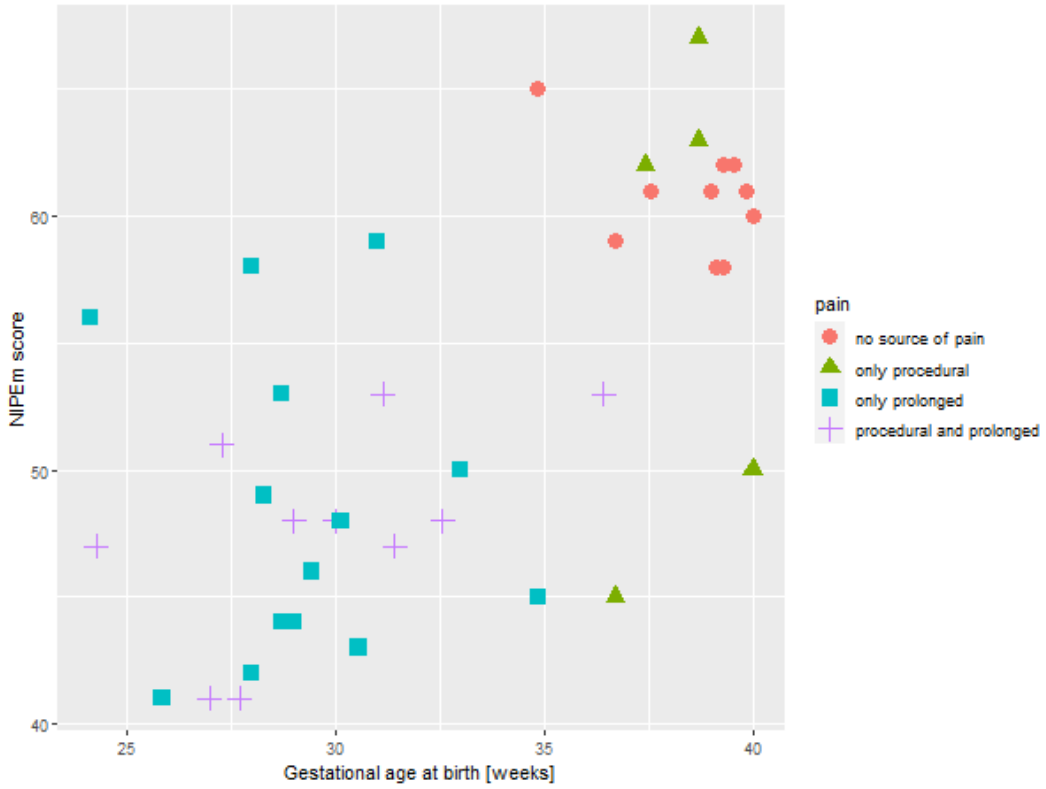


Figure 6. The NIPEm score vs. gestational age at birth, all patients (N = 40).

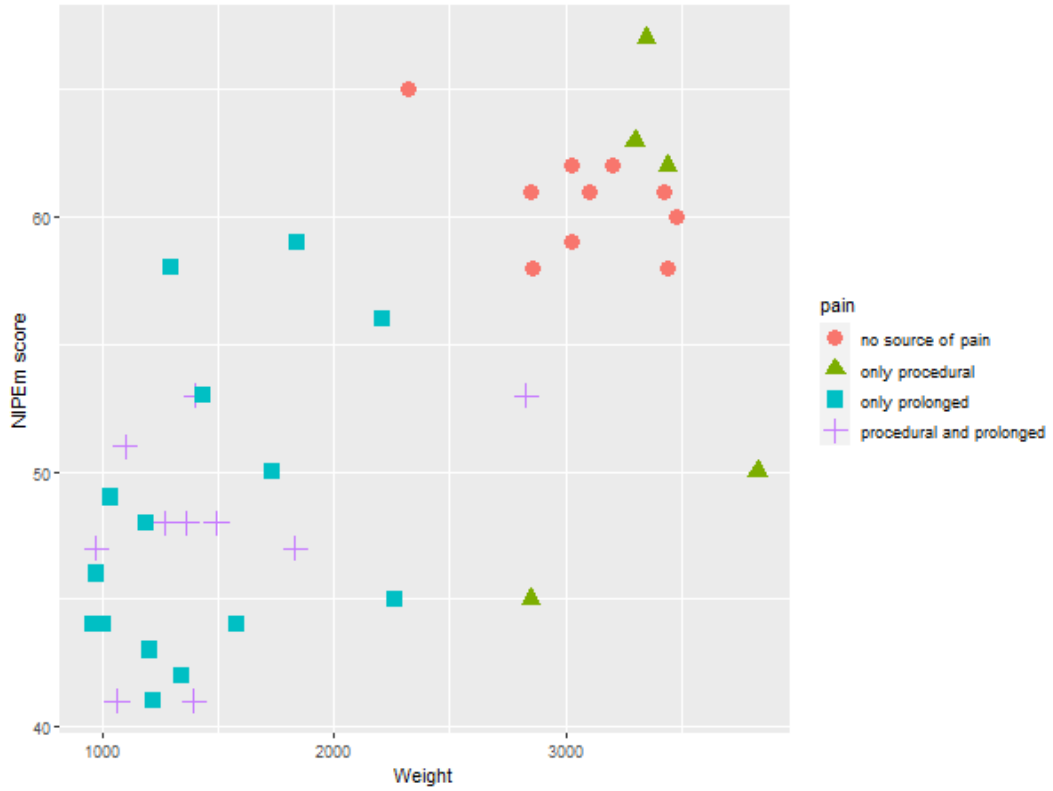


Figure 7. The NIPEm score vs. weight, all patients (N = 40).

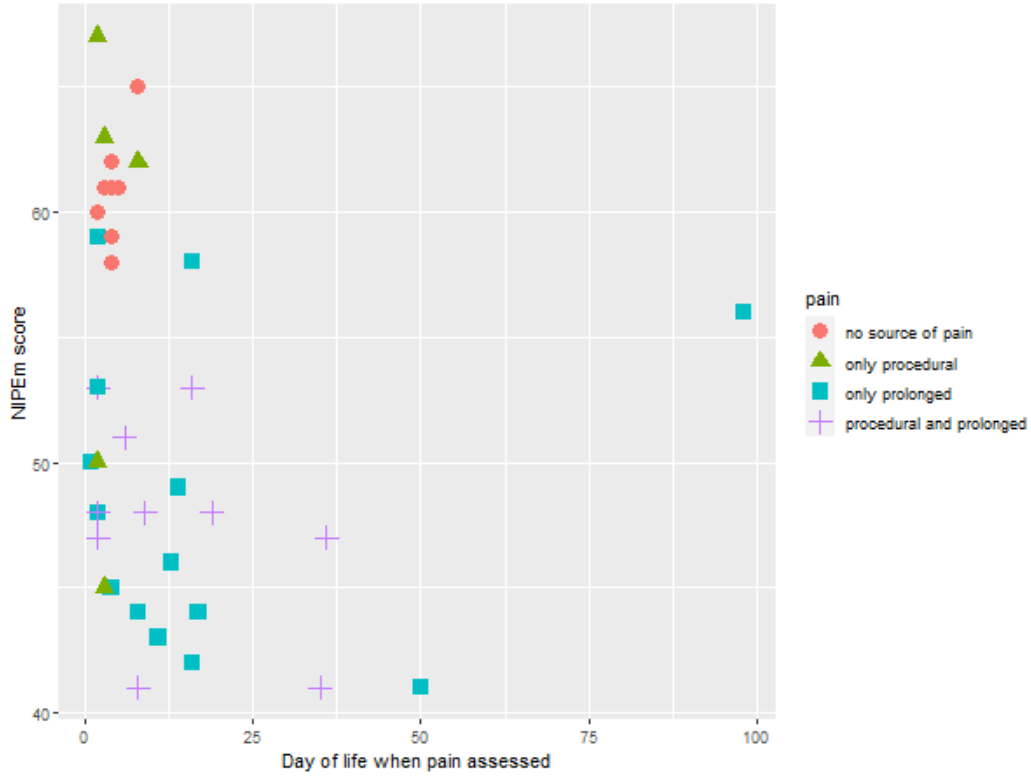


Figure 8. The NIPEm score vs. day of life when pain assessed, all patients (N = 40)

7. ANALYSIS OF THE FACTORS INLUENCING NIPEm SCORE IN THE EXPERIMENTAL GROUPS WITH PROLONGED AND/OR PROCEDURAL PAIN

Table 16. The NIPEm score vs. gender, patients with any source of pain (N=30)

NIPEm score vs. gender, patients with any source of pain	N	Overall, N = 30	Male, N = 16	Female, N = 14	p-value[1]
NIPEm	30				0.900
Mean (SD)		49.5 (6.9)	50.1 (8.2)	48.9 (5.2)	
Median (Range)		48.0 (41.0, 67.0)	49.0 (41.0, 67.0)	48.0 (42.0, 59.0)	

[1]Wilcoxon rank sum test

There is no significant difference in the NIPEm score between male and female neonates with any source of pain.

Evaluated newborns were divided in four groups depending on their gestational age at birth to assess the age at birth as the influencing factor in the NIPEm, NIPEi results and to evaluate patients' sensitivity to pain according to their age group:

- extremely preterm neonates: 24week 0/7days – 27weeks 6/7days GA,
- very preterm neonates: 28weeks 0/7days – 31weeks 6/7 days GA,
- moderate to late preterm neonates: 32weeks 0/7days – 36weeks 6/7days GA,
- full-term neonates: 37weeks 0/7 days – 42weeks 6/7 days GA.

Table 17. The NIPEm score vs. gestational age at birth (categorical), patients with any source of pain (N=30).

NIPEm score vs. gestational age at birth (categorical), patients with any source of pain	N	Overall, N = 30	full-term, N = 4	moderate or late preterm, N = 5	very preterm, N = 15	extremely preterm, N = 6	p-value[1]
NIPEm	30						0.039
Mean (SD)		49.5 (6.9)	60.5 (7.3)	48.2 (3.4)	48.4 (5.2)	46.2 (6.3)	
Median (Range)		48.0 (41.0, 67.0)	62.5 (50.0, 67.0)	48.0 (45.0, 53.0)	48.0 (42.0, 59.0)	44.0 (41.0, 56.0)	

[1]Kruskal-Wallis rank sum test

There is statistically significant difference in the NIPEm score (p-value = 0.039) between full term, moderate or late preterm, very preterm and extremely preterm neonates with any source of pain.

Table 18. Univariate linear models for the NIPEm, patients with any source of pain (N = 30).

Characteristic	N	Beta	95% CI[1]	p-value
Gestational age at birth	30	0.76	0.22, 1.3	0.007
Gestational age at birth categorical	30			
full-term		—	—	
moderate or late preterm		-12	-20, -4.7	0.003
very preterm		-12	-18, -5.7	<0.001
extremely preterm		-14	-22, -7.0	<0.001
Weight in kg	30	4.8	2.3, 7.3	<0.001
Day of life when pain assessed	30	-0.03	-0.17, 0.10	0.633

[1]CI = Confidence Interval

Among neonates with any source of pain, significant factors influencing the NIPEm result were gestational age at birth and weight. The mean NIPEm score was 4.8 points higher with each kilogram and 0.76 points higher with each week of gestational age at birth. Moderate and late preterm and very preterm neonates had 12 points less (on average) in the NIPEm score than full term neonates. Extremely preterm neonates had 14 points less (on average) in the NIPEm score than full term neonates.

8. THE NIPEm SCORE VS. PATIENTS' CHARACTERISTICS IN THE EXPERIMENTAL GROUP WITH PROLONGED PAIN

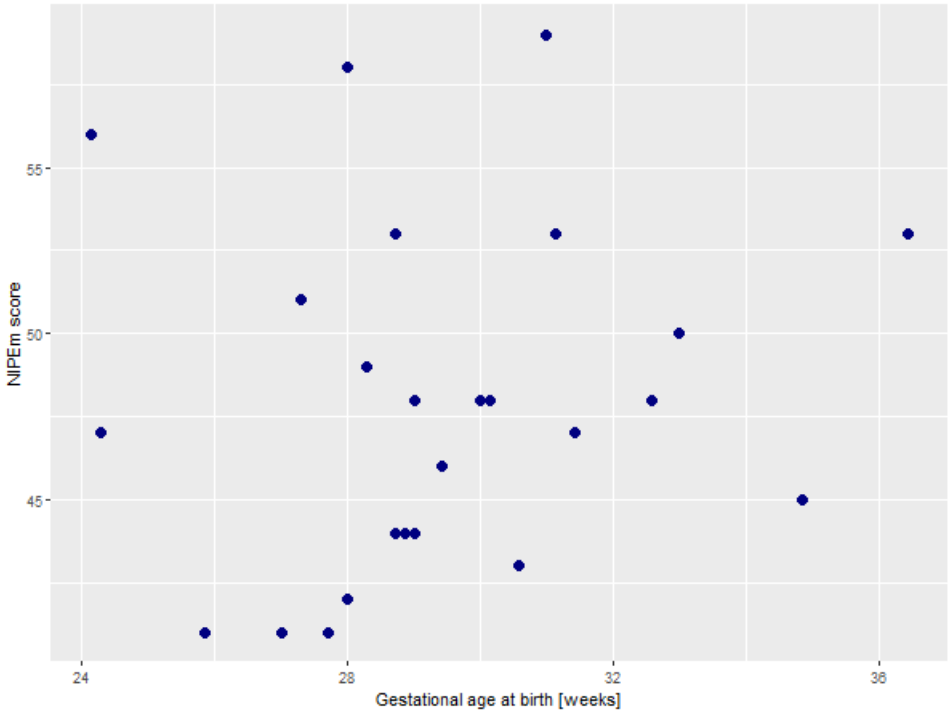


Figure 9. The NIPEm score vs. gestational age at birth, patients with prolonged pain (N = 25).

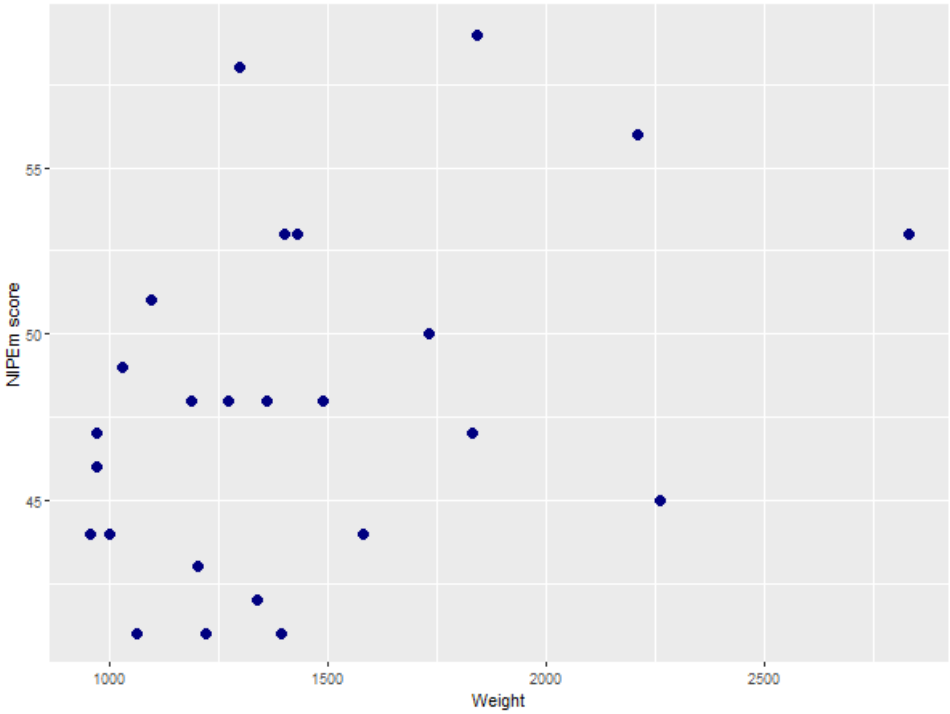


Figure 10. The NIPEm score vs. weight, patients with prolonged pain (N=25).

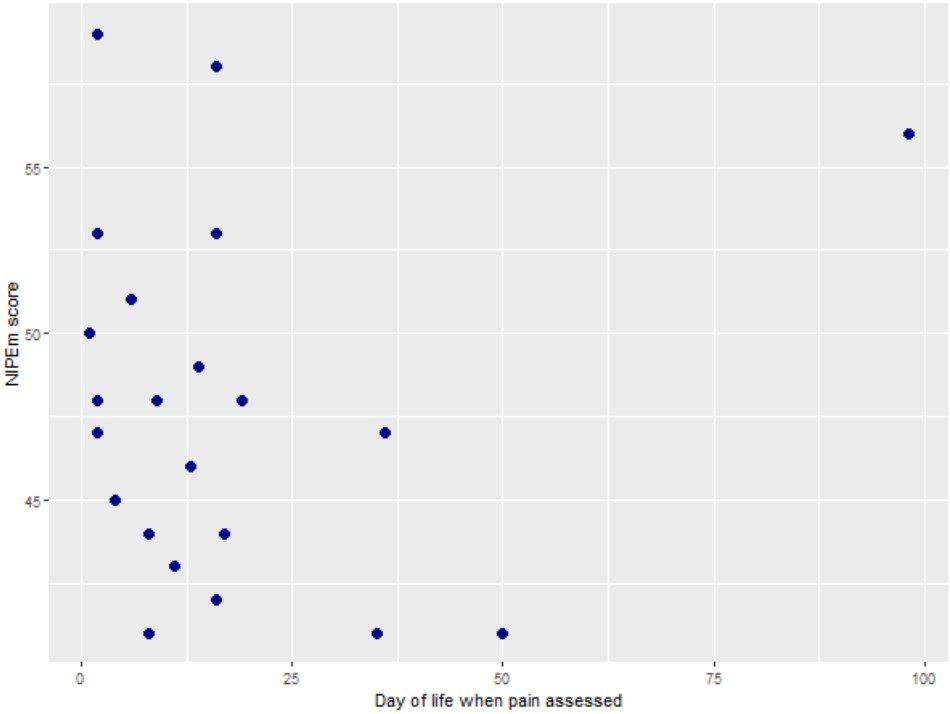


Figure 11. The NIPEm score vs. day of life when pain assessed, patients with prolonged pain (N = 25).

Table 19. The NIPEm score vs. gender, patients with prolonged pain (N=25).

NIPEm score vs. gender, patients with prolonged pain	N	Overall, N = 25	Male, N = 11	Female, N = 14	p-value[1]
NIPEm	25				0.350
Mean (SD)		48.0 (5.2)	46.8 (5.2)	48.9 (5.2)	
Median (Range)		48.0 (41.0, 59.0)	46.0 (41.0, 56.0)	48.0 (42.0, 59.0)	

[1]Wilcoxon rank sum test

There is no significant difference in the NIPEm score (p-value = 0.35) between male and female neonates with prolonged source of pain.

Table 20. The NIPEm score vs. gestational age at birth, patients with prolonged pain (N=25).

NIPEm score vs. gestational age at birth (categorical), patients with prolonged pain	N	Overall, N = 25	full-term, N = 0	moderate or late preterm, N = 4	very preterm, N = 15	extremely preterm, N = 6	p-value[1]
NIPEm	25						0.437
Mean (SD)		48.0 (5.2)	-	49.0 (3.4)	48.4 (5.2)	46.2 (6.3)	
Median (Range)		48.0 (41.0, 59.0)	-	49.0 (45.0, 53.0)	48.0 (42.0, 59.0)	44.0 (41.0, 56.0)	

[1]Kruskal-Wallis rank sum test

There is no statistically significant difference in the NIPEm score (p-value = 0.437) between full term, moderate or late preterm, very preterm and extremely preterm neonates with prolonged pain.

Table 21. The NIPEm score vs. ventilation type, patients with prolonged pain (N=25).

NIPEm score vs. ventilation type, patients with prolonged pain	N	Overall, N = 25	invasive, N = 4	non-invasive, N = 21	p-value[1]
NIPEm	25				0.710
Mean (SD)		48.0 (5.2)	49.2 (6.7)	47.7 (5.0)	
Median (Range)		48.0 (41.0, 59.0)	50.0 (41.0, 56.0)	48.0 (41.0, 59.0)	

[1]Wilcoxon rank sum test

There is no statistically significant difference in the NIPEm score (p-value = 0.71) between neonates with invasive and non-invasive ventilation as a source of prolonged pain.

Table 22. Univariate linear models for the NIPEm, patients with prolonged pain (N = 25).

Characteristic	N	Beta	95% CI[1]	p-value
Gestational age at birth	25	0.25	-0.51, 1.0	0.500
Gestational age at birth categorical	25			
moderate or late preterm		—	—	
very preterm		-0.60	-6.8, 5.6	0.842
extremely preterm		-2.8	-9.9, 4.3	0.417
Weight in kg	25	4.5	0.03, 8.9	0.048
Day of life when pain assessed	25	0.01	-0.10, 0.12	0.847
Ventilation type	25			
Invasive		—	—	
non-invasive		-1.5	-7.5, 4.4	0.598

[1]CI = Confidence Interval

Among neonates with prolonged pain, the only significant factor influencing the NIPEm result was weight.

The mean NIPEm score was 4.5 points higher with each kilogram.

9. ANALYSIS OF NIPE SCORES IN THE EXPERIMENTAL GROUP WITH PROCEDURAL PAIN

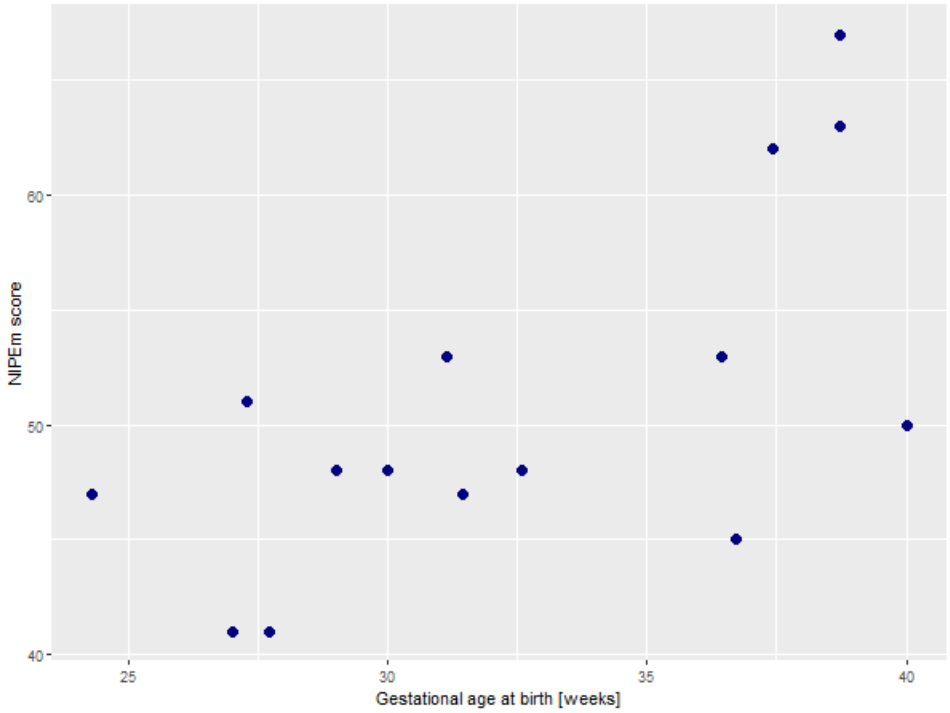


Figure 12. The NIPEm score vs. gestational age at birth, patients with procedural source of pain (N = 15).

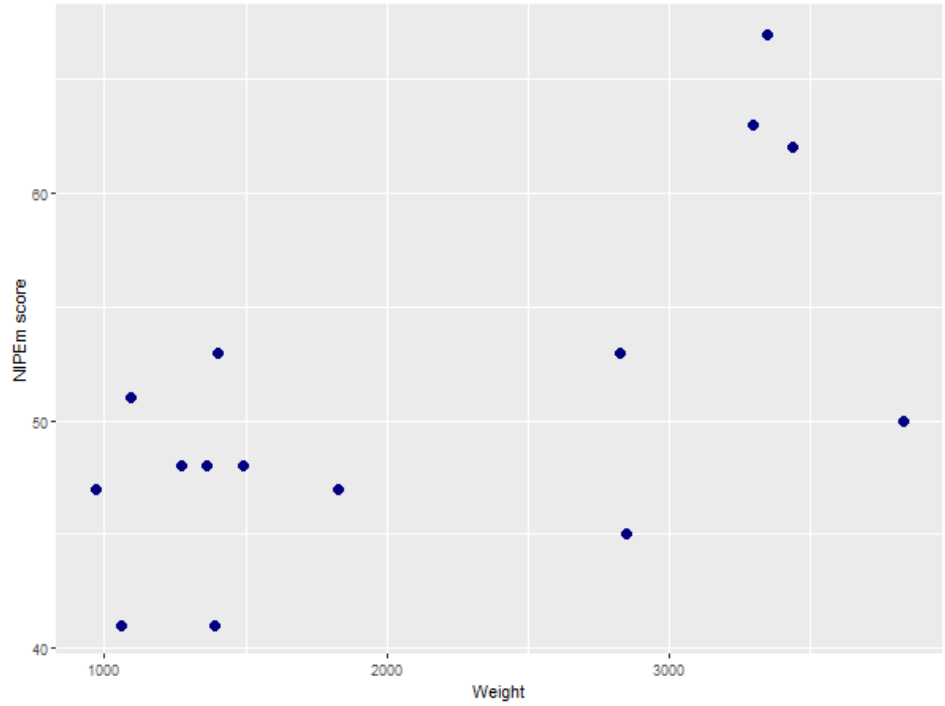


Figure 13. The NIPEm score vs. weight, patients with procedural source of pain (N = 15).

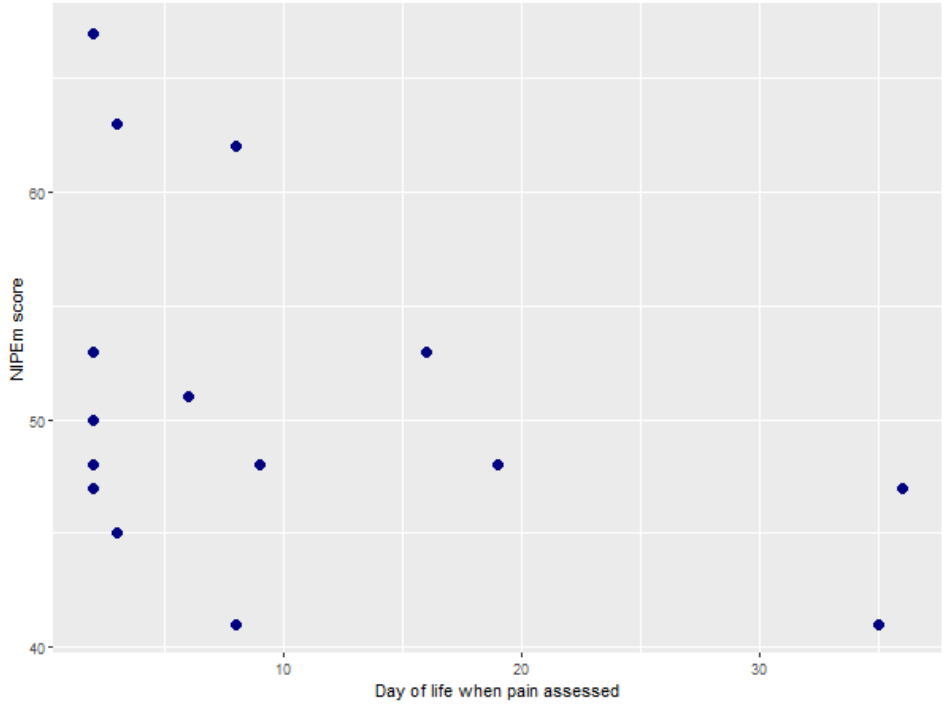


Figure 14. The NIPEm score vs. day of life when pain assessed, patients with procedural source of pain (N = 15).

Table 23. NIPE scores vs. gender, patients with procedural pain (N=15).

NIPE scores vs. gender, patients with procedural source of pain	**N**	**Overall, N = 15**	**Male, N = 10**	**Female, N = 5**	**p-value[1]**
NIPEm	15				0.538
Mean (SD)		50.9 (7.7)	52.1 (9.2)	48.6 (2.5)	
Median (Range)		48.0 (41.0, 67.0)	50.5 (41.0, 67.0)	48.0 (47.0, 53.0)	
NIPEi minimum	15				0.623
Mean (SD)		35.4 (11.8)	37.4 (13.7)	31.4 (6.2)	
Median (Range)		30.0 (22.0, 59.0)	33.5 (22.0, 59.0)	30.0 (27.0, 42.0)	
NIPEm 20 min. after painful procedure	15				0.389
Mean (SD)		52.5 (8.8)	54.4 (10.0)	48.6 (4.3)	
Median (Range)		51.0 (41.0, 74.0)	52.5 (41.0, 74.0)	50.0 (42.0, 53.0)	
Decrease of NIPE index [%]	15				0.759
Mean (SD)		31.6 (15.1)	29.9 (15.7)	35.0 (14.7)	
Median (Range)		36.2 (10.6, 49.1)	33.8 (11.1, 46.3)	36.2 (10.6, 49.1)	

[1]Wilcoxon rank sum test

There is no significant difference in the NIPEm score, the minimum NIPEi score, the NIPEm score 20 minutes after painful procedure and the percentage decrease of the NIPE index between male and female neonates with procedural source of pain.

Table 24. NIPE scores vs. gestational age at birth (categorical), patients with procedural pain (N=15).

NIPE score vs. gestational age at birth (categorical), patients with procedural source of pain	**N**	**Overall, N = 15**	**full-term, N = 4**	**moderate or late preterm, N = 3**	**very preterm, N = 4**	**extremely preterm, N = 4**	**p-value[1]**
NIPEm	15						0.061
Mean (SD)		50.9 (7.7)	60.5 (7.3)	48.7 (4.0)	49.0 (2.7)	45.0 (4.9)	
Median (Range)		48.0 (41.0, 67.0)	62.5 (50.0, 67.0)	48.0 (45.0, 53.0)	48.0 (47.0, 53.0)	44.0 (41.0, 51.0)	
NIPEi minimum	15						0.033
Mean (SD)		35.4 (11.8)	50.8 (9.6)	33.7 (5.5)	28.0 (1.4)	28.8 (9.4)	
Median (Range)		30.0 (22.0, 59.0)	53.5 (37.0, 59.0)	31.0 (30.0, 40.0)	27.5 (27.0, 30.0)	25.5 (22.0, 42.0)	
NIPEm 20 min. after painful procedure	15						0.032
Mean (SD)		52.5 (8.8)	64.5 (6.5)	49.3 (2.9)	49.2 (2.9)	46.0 (5.9)	
Median (Range)		51.0 (41.0, 74.0)	62.0 (60.0, 74.0)	51.0 (46.0, 51.0)	48.5 (47.0, 53.0)	44.5 (41.0, 54.0)	
Decrease of NIPE index [%]	15						0.174
Mean (SD)		31.6 (15.1)	16.7 (6.8)	30.0 (16.8)	42.7 (5.3)	36.6 (17.4)	
Median (Range)		36.2 (10.6, 49.1)	14.7 (11.3, 26.0)	35.4 (11.1, 43.4)	42.7 (36.2, 49.1)	44.7 (10.6, 46.3)	

[1]Kruskal-Wallis rank sum test

There is statistically significant difference in the NIPEm score (p-value = 0.061) between full term, moderate or late preterm, very preterm and extremely preterm neonates with procedural pain.

There is statistically significant difference in the minimum NIPEi score (p-value = 0.033) between full term, moderate or late preterm, very preterm and extremely preterm neonates with procedural pain.

There is statistically significant difference in the NIPEm score 20 minutes after painful procedure (p-value = 0.032) between full term, moderate or late preterm, very preterm and extremely preterm neonates with procedural pain.

There is no statistically significant difference in percentage decrease of NIPE score (p-value = 0.174) between full term, moderate or late preterm, very preterm and extremely preterm neonates with procedural pain.

Table 25. NIPE scores vs. type of procedural pain, patients with procedural pain (N=15).

NIPE score vs. type of procedural pain, patients with procedural source of pain	**N**	**Overall, N = 15**	**heel lancing, N = 8**	**vena puncturing, N = 2**	**suction, N = 4**	**cleaning of injuried skin around external nostrils, N = 1**	**p-value[1]**
NIPEm	15						0.353
Mean (SD)		50.9 (7.7)	51.4 (9.1)	56.0 (8.5)	50.0 (2.4)	41.0 (NA)	
Median (Range)		48.0 (41.0, 67.0)	47.5 (41.0, 67.0)	56.0 (50.0, 62.0)	49.5 (48.0, 53.0)	41.0 (41.0, 41.0)	
NIPEi minimum	15						0.142
Mean (SD)		35.4 (11.8)	37.9 (12.8)	46.0 (12.7)	28.5 (1.3)	22.0 (NA)	
Median (Range)		30.0 (22.0, 59.0)	35.5 (22.0, 59.0)	46.0 (37.0, 55.0)	28.5 (27.0, 30.0)	22.0 (22.0, 22.0)	
NIPEm 20 min. after painful procedure	15						0.287
Mean (SD)		52.5 (8.8)	50.9 (8.1)	67.0 (9.9)	49.8 (3.4)	47.0 (NA)	
Median (Range)		51.0 (41.0, 74.0)	50.5 (41.0, 63.0)	67.0 (60.0, 74.0)	49.0 (47.0, 54.0)	47.0 (47.0, 47.0)	
Decrease of NIPE index [%]	15						0.217
Mean (SD)		31.6 (15.1)	27.3 (16.3)	18.6 (10.4)	43.0 (0.9)	46.3 (NA)	
Median (Range)		36.2 (10.6, 49.1)	26.4 (10.6, 49.1)	18.6 (11.3, 26.0)	43.3 (41.7, 43.8)	46.3 (46.3, 46.3)	

[1]Kruskal-Wallis rank sum test

There is no significant difference in the NIPEm score, the minimum NIPEi score, the NIPEm score 20 minutes after painful procedure and the percentage decrease of the NIPE index between neonates with various types of procedural pain.

Table. 26. Univariate linear models for the NIPEm, patients with procedural pain (N = 15).

Characteristic	N	Beta	95% CI[1]	p-value
Gestational age at birth	15	1.0	0.31, 1.7	0.008
Gestational age at birth categorical	15			
full-term		—	—	
moderate or late preterm		-12	-20, -3.2	0.011
very preterm		-12	-19, -3.5	0.009
extremely preterm		-16	-23, -7.5	0.001
Weight in kg	15	4.9	1.5, 8.2	0.008
Day of life when pain assessed	15	-0.26	-0.63, 0.10	0.145
Type of procedural pain	15			
heel lancing		—	—	
vena puncturing		4.6	-9.0, 18	0.469
Suction		-1.4	-12, 9.1	0.779
cleaning of injuried skin around external nostrils		-10	-29, 7.8	0.236

[1]CI = Confidence Interval

Among neonates with procedural pain, significant factors influencing the NIPEm result were gestational age at birth and weight.

The mean NIPEm score was 4.9 points higher with each kilogram and 1 point higher with each week of gestational age at birth.

Moderate and late preterm and very preterm neonates had 12 points less (on average) in the NIPEm score than full term neonates. Extremely preterm neonates had 16 points less (on average) in the NIPEm score than full term neonates.

Table 27. Univariate linear models for the minimum NIPEi, patients with procedural pain (N = 15).

Characteristic	N	Beta	95% CI[1]	p-value
Gestational age at birth	15	1.5	0.42, 2.6	0.010
Gestational age at birth categorical	15			
full-term		—	—	
moderate or late preterm		-17	-30, -4.6	0.012
very preterm		-23	-34, -11	0.001
extremely preterm		-22	-34, -10	0.002
Weight in kg	15	8.2	3.5, 13	0.003
Day of life when pain assessed	15	-0.26	-0.86, 0.33	0.358
Type of procedural pain	15			
heel lancing		—	—	
vena puncturing		8.1	-11, 27	0.367
suction		-9.4	-24, 5.4	0.189
cleaning of injuried skin around external nostrils		-16	-41, 9.6	0.198

[1]CI = Confidence Interval

Among neonates with procedural pain, significant factors influencing the minimum NIPEi result were gestational age at birth and weight.

The minimal NIPEi score was 8.2 points higher with each kilogram (on average) and 1.5 points higher with each week of gestational age at birth.

Moderate and late preterm neonates had 17 points less (on average) in the minimal NIPEi score than full term neonates.

Very preterm neonates had 23 points less (on average) in the minimal NIPEi score than full term neonates.

Extremely preterm neonates had 22 points less (on average) in the minimal NIPEi score than full term neonates.

Table 28. Univariate linear models for the NIPEm 20 minutes after painful procedure, patients with procedural pain (N = 15).

Characteristic	N	Beta	95% CI[1]	p-value
Gestational age at birth	15	1.3	0.69, 2.0	<0.001
Gestational age at birth categorical	15			
full-term		—	—	
moderate or late preterm		-15	-24, -6.8	0.002
very preterm		-15	-23, -7.5	0.001
extremely preterm		-19	-26, -11	<0.001
Weight in kg	15	6.6	3.4, 9.9	<0.001
Day of life when pain assessed	15	-0.45	-0.82, -0.08	0.021
Type of procedural pain	15			
heel lancing		—	—	
vena puncturing		16	3.4, 29	0.018
suction		-1.1	-11, 8.7	0.806
cleaning of injuried skin around external nostrils		-3.9	-21, 13	0.627

[1]CI = Confidence Interval

Among neonates with procedural pain, significant factors influencing the NIPEm result 20 minutes after painful procedure were: gestational age at birth, weight, day of life when pain was assessed and procedural pain from vena puncturing.

The NIPEm result 20 minutes after painful procedure was 6.6 points higher with each kilogram (on average) and 1.3 points higher with each week of gestational age at birth.

Moderate and late preterm and very preterm neonates had 15 points less (on average) in the NIPEm result 20 minutes after painful procedure than full term neonates.

Extremely preterm neonates had 19 points less (on average) in the NIPEm result 20 minutes after painful procedure than full term neonates.

The NIPEm result 20 minutes after painful procedure was 0.45 points lower with each day of life (on average).

Patients whose source of pain was vena puncturing had 16 points more (on average) in the NIPEm result 20 minutes after painful procedure than patients whose source of pain was heel lancing.

Table 29. Univariate linear models for the decrease of NIPE index [%], patients with procedural pain (N = 15).

Characteristic	N	Beta	95% CI[1]	p-value
Gestational age at birth	15	-1.5	-3.0, 0.09	0.062
Gestational age at birth categorical	15			
full-term		—	—	
moderate or late preterm		13	-7.6, 34	0.188
very preterm		26	6.7, 45	0.013
extremely preterm		20	0.62, 39	0.044
Weight in kg	15	-8.9	-16, -1.9	0.017
Day of life when pain assessed	15	0.14	-0.64, 0.92	0.710
Type of procedural pain	15			
heel lancing		—	—	
vena puncturing		-8.6	-32, 15	0.432
suction		16	-2.3, 34	0.081
cleaning of injuried skin around external nostrils		19	-12, 50	0.205

[1]CI = Confidence Interval

Among neonates with procedural pain, significant factors influencing the percentage decrease of NIPE index were: gestational age at birth and weight.

The percentage decrease of NIPE index was 8.9 percentage points lower with each kilogram (on average) and 1.5 percentage points lower with each week of gestational age at birth.

Very preterm neonates had 26 percentage points more (on average) in the decrease of NIPE index than full term neonates.

Extremely preterm neonates had 20 percentage points more (on average) in the decrease of NIPE index than full term neonates.

1. SUMMARY OF RESULTS

40 patients (21 male neonates and 19 female neonates) were included in the study of pain: 25 patients were assessed in the first experimental group of ventilated preterm newborns, 15 patients were evaluated while experiencing acute procedural pain and the control group consisted of 10 patients in comfort and without any source of pain.

The analysis of results of the first experimental group of patients assessed with behavioral scales N-PASS, PIPP and EDIN and also with the NIPE pain monitor confirmed that ventilated patients may potentially feel pain: according to the N-PASS score 17 patients (68.0%) out of 25 ventilated neonates were experiencing pain during observation, on the basis of results of the PIPP scale 19 (76%) newborns were in pain, the EDIN results showed that 17 patients (68%) were feeling pain. The NIPE monitor detected pain and discomfort in 18 neonates (72%).

The correlation analysis between behavioral pain assessment scales and the NIPEm results confirmed that there is very strong and high significant negative Spearman correlation between the N-PASS score and the NIPEm score (p value < 0,001), the PIPP score and the NIPEm score (p value 0,002), the EDIN score and the NIPEm score (p value < 0,001). Calculated accuracy for pain scales and the NIPEm index showed very high agreement: between the N-PASS score and the NIPEm score (Cohen's kappa = 0.905, accuracy = 96%), the PIPP score and the NIPEm score (Cohen's kappa = 0.689, accuracy = 88%), the EDIN score and the NIPEm score (Cohen's kappa = 0.905, accuracy = 96%).

All these three pain scales have been validated before and are commonly used worldwide for pain evaluation in newborns. The above results of correlations with the NIPEm index proved that the NIPE pain monitor is a reliable tool for pain assessment in preterm newborns experiencing acute prolonged pain.

Neonates subjected to acute procedural pain were assessed only with the NIPE pain monitor. Their sensitivity to pain was evaluated according to their gestational age at birth with the decrease of NIPE index (to examine what was the difference between the NIPEm median result and the minimal NIPEi) and analysing NIPEi results recorded up to 3 min. after painful stimuli.

There was statistically significant difference in the minimum NIPEi results during the evaluation between full term, moderate or late preterm, very preterm and extremely preterm neonates with procedural pain (p-value = 0,033). The decrease of NIPE index was generally higher in neonates born prematurely than in term newborns: the mean score of the decrease of NIPE index were: for extremely preterm newborns 36.6%, very preterm 42.7%, moderately or late preterm 30.0% and full-term babies 16,7% which would suggest that preterm babies are more sensitive to pain than term-babies.

Moreover there was statistically significant difference in the NIPEm scores 20 min. after painful procedures (p-value = 0.032) between different age groups of newborns. Extremely preterm neonates had the lowest mean NIPEm score 20min. after painful stimuli 46.0; very preterm 49.2; moderate or late preterm 49.3; full-term 64.5. It could mean that the youngest children feel pain more severely with longer nociceptive effects of performed painful procedure.

The NIPE scores recorded while observing patients with procedural pain were not influenced by gender or the type of procedural pain. There was no significant difference in the NIPE scores in relation to these factors.

The analysis of the patients results showed that not only the gestational age at birth but also the weight was the factor that had influence on the NIPE results.

The NIPE scores recorded while monitoring preterm ventilated patients were not influenced by gender or the mode of ventilation. There was no significant difference in the NIPE scores in relation to these factors.

There was no statistically significant difference in the NIPEm scores (p-value = 0,437) between patients experiencing prolonged pain according to their age. However the mean NIPEm result in the extremely preterm newborns was the lowest – 46.2; in the very preterm babies the mean NIPEm score was 48.4 and in the moderate or late preterm group of neonates – 49.0.

The control group of healthy newborns not subjected to any noxious stimuli during their observation was assessed only with the NIPE pain monitor. Their mean NIPEm score was 60.7 (range 58.0 – 65.0). According to patients' results obtained from the NIPE monitor no one felt pain (100%). The NIPEm score was significantly lower in the experimental group with any source of pain than in the control group (p-value <0,001).

VII. DISCUSSION

Monitors to assess pain in neonates are becoming more popular in NICUs. There is a few available options of monitoring pain including skin conductance, near infrared spectroscopy, electroencephalography and with the Newborn Infant Parasympathetic Evaluation monitor that uses heart rate variability. None of them has become prime in the diagnosis of newborns' pain. In studies of pain assessment in newborns researchers emphasize that they are imperfect and many times poor inter-observer agreement score limits the data of their findings. Pain assessment in neonates is presently mainly based on pain scales that also have their drawbacks and are not free from bias. Reliable assessment tools are essential for proper management of pain and increasing the quality of newborns' care.

Behavioral scales for pain assessment in newborns have been thoroughly studied especially during last 30 years. Mainly behavioral scales were invented for evaluation of acute pain to provide adequate pain relief instantly. Only a few have been validated for assessment of prolonged pain and several for ventilated patients. Developing objective and accurate method to monitor these patients is very challenging.

Ventilated neonates experiencing prolonged pain were assessed with two behavioral pain scales conducted by Desai et al. in 2017. The results of the Neonatal Pain, Agitation and Sedation Scale (N-PASS) and the Premature Infant Pain Profile scale (PIPP) were analyzed. 15 neonates of gestational age 34.3 ± 4.56 were scored during invasive or non-invasive ventilation. This research confirmed that ventilation may be the source of prolonged pain in neonates. The results of the N-PASS scale and the PIPP scale were comparable.

In 2018 Huang et al. published the results of their study evaluating three pain scales used for ventilated neonates. The Neonatal Pain, Agitation and Sedation Scale (N-PASS), the Neonatal Infant Acute Pain Assessment Scale (NIAPAS) and the Premature Infant Pain Profile-Revised scale (PIPP-R) were used for evaluating 90. preterm and term newborns. All three scales proved to be valid and reliable to assess ventilated newborns, the correlation between them was strong. According to performed analysis the excellent inter-raters coefficients and good internal consistency was proved as well for all three scales. The N-PASS scale was a preferable scale in opinion of nurses [96].

This is one of the latest study assessing pain in ventilated neonates with behavioral scales. Even though their utility and reliability was confirmed with studies conducted up to now, the pain scales are underutilized at neonatal intensive care units for many reasons. They do not allow to monitor patients constantly, they are time-consuming and difficult to implement for daily routine at NICUs. Moreover the subjectivity of rating is the limit and none of the pain scales is recommended as gold standard.

Heart rate variability is one of the most thoroughly studied parameter in newborns for various purposes [45, 120]. It has been a relevant tool to assess especially the autonomic nervous system [93, 129, 154]. High HRV is associated with good health and decreased level of stress in patients [119]. Decreased HRV can be the result of pain in newborns. What is more the usefulness of HRV in detecting and assessing pain is beyond doubt on the basis of available data from many studies conducted in neonates. Heart rate variability has emerged as non-invasive method to monitor newborns. It correlates with newborn's stress and stress-related conditions.

Unfortunately there is many factors that can influence HRV: heart rate, gender, blood pressure, health status, hypoxia and ventilation, diseases, maturation of the autonomic nervous system (age), mode of delivery and many drugs [43, 110, 124, 161, 163]. HRV parameters observed in newborns of different gestational age are lower in the youngest neonates [41, 63, 70, 111, 174]. Autonomic disfunction and the results of HRV are inversely correlated with organ dysfunction in organ disfunction or sepsis [19]. Heart rate variability can be useful to evaluate patient's state, the risk of deterioration and generally to identify system instability even before any clinical signs are visible.

The environmental and physiological conditions can have impact on HRV as well, including circadian rhythms, the sleep cycle, the time of the day. So the background setting should be established while assessing patients with HRV.

Heart rate variability in newborns was studied vastly by Prof. Kamil Javorka who confirmed that the maturity of the parasympathetic innervation of the heart depends on the gestational age of the patient. Respiratory distress syndrome may also have impact on HRV causing its low results. Other possible determinants of decreased HRV observed by Javorka were clinically significant patent ductus arteriosus, congenital heart defects, neonatal sepsis,

caesarean section delivery, hypotrophy and hypoxic ischemic encephalopathy [100, 101]. During traumatic brain injury or seizures the loss of HRV can occur too [149].

A few researches in the topic of heart rate variability in ventilated preterm neonates were carried out by Ravenswaaij-Arts et al. [159, 160, 162] The findings suggested that HRV could be a promising method of neonatal monitoring during ventilation.

The analysis of heart rate variability for the newborn pain assessment was studied by Jonckheere et al. The magnitude of the heart rate high frequency variations was measured in 28 neonates at risk of postoperative prolonged pain. Children of mean gestational age 37.8 ± 1.5 weeks after major surgical procedure including thoracotomy and laparotomy were evaluated with the EDIN scale and their heart rate variabilities were analyzed with the High Frequency Variability Index (HFVI) invented for pain assessment. The HFVI results correlated with the EDIN scores [64]. In another study of Jonckheere heart rate variability calculation was performed for newborns experiencing prolonged pain. 41 infants were assessed with the EDIN scale and instantaneous HRV analysis that was recommended for newborns with prolonged pain for further clinical investigation [56].

Heart rate variability can be valuable for monitoring newborns in neonatal intensive care units. For over 40 years of medical progress its reliability for assessing neonates has been established. Although the method of measurement was the essential limitation, the new technology allowed the utilization of the analysis of heart rate variability for creating the device that visualize the patient's results on monitor supporting the neonatal care.

The NIPE pain monitor was developed in 2015. Pain and stress in newborns can influence sympathetic and parasympathetic responses of autonomic nervous system activity and heart rate variability can be measured by the variations of RR variations [35]. The NeoDoloris project of French researchers adapted the automatic analysis of neonatal HRV in high frequencies, that is representative for the parasympathetic activity for inventing the Newborn Infant Parasympathetic Evaluation index and the NIPE pain monitor displaying it to visualize patient's level of pain and discomfort. The NIPE pain monitor was recommended to use particularly at the neonatology department to support newborns medical care to monitor the pain as the fifth vital sign at the bedside. Since that time several studies were carried out to assess its clinical utility and validity with various results [35].

Nevertheless the usefulness, reliability and validity of the NIPE pain monitor is still questioned by clinicians because of the limited available data.

The main objective of this study was to establish the utility of the NIPE pain monitor and to assess its reliability to evaluate pain in newborns in different potentially painful clinical settings at the department of neonatology. In this study the NIPE monitor was tested to evaluate preterm babies potentially being in discomfort and experiencing acute prolonged pain due to ventilation and in the second sub-study it was used for assessment of children's pain sensitivity to acute procedural noxious stimuli.

In the first sub-study the results of assessment with three behavioral well-known pain scales were compared with the Newborn Infant Parasympathetic Evaluation index to establish its reliability and utility for monitoring ventilated preterm babies. The correlation analysis of all results showed that there is very strong and high significant correlation between the N-PASS score, the EDIN score, the PIPP score and the NIPEm result. The NIPEm result is advised to be used for assessment of prolonged pain. In the clinical situation of non-invasive and invasive ventilation it is presumed that babies are in discomfort. The NIPEm results of 18 patients (72%) proved that assisted ventilation can be the source of prolonged pain. Calculated accuracy for pain scales and the NIPEm index showed very high agreement between them. It was confirmed that the NIPE pain monitor is valid, reliable and useful tool at the department of neonatology to assess preterm babies and to evaluate pain and discomfort during ventilation.

Prolonged pain in preterm infants was also studied for patients with pneumothorax using heart rate variability and the EDIN behavioral scale (Buyuktiryaki et al). The patients were monitored with the NIPE pain monitor as well. 23 preterm babies at the age between 33 and 35 of gestational week at birth were enrolled for that trial. A significant correlation between the EDIN scores and the NIPE index was also observed [36].

The Newborn Infant Parasympathetic Evaluation Index derived from heart rate variability was used in one trial (Verweij et al.) for monitoring early postoperative pain and discomfort in 121 patients (age 0 - 2 years). The NIPE index results were compared with the FLACC score and the COMFORT score. The NIPE was useful for detecting pain in infants after general

anesthesia although the data suggested limited value of the NIPE pain monitor as a predictor of the scores of behavioral pain scales [208].

The NIPE pain monitor was also used in the study of Walas et al. to assess analgosedation in mechanically ventilated patients. 30 babies (postmenstrual age at the time of trial 36 – 42 weeks; gestational age at birth 33 – 38 weeks) were included in that research. Children were evaluated with the COMFORT-B scale too. The results of the study confirmed that the NIPE scores are related to the levels of analgosedation. The NIPE indexes were significantly higher in infants deeply sedated.

The studies of preterm neonates with prolonged pain using the NIPE index are very limited. Therefore the results of this study of pain in newborns give valuable additional data on its utility in the clinical situation of ventilated infants potentially experiencing prolonged pain and discomfort.

The aim of the second part of the study was to assess newborns sensitivity to acute painful stimuli in relation to their gestational age at birth. So far this was the first study to evaluate it with the NIPE index. Statistically significant difference in the minimum NIPEi results between full term, moderate to late preterm, very preterm and extremely preterm newborns experiencing acute procedural pain was confirmed (p-value = 0,033). The decrease of NIPE index was higher generally in preterm neonates in comparison with full-term babies and it suggests that premies are more sensitive to painful stimuli that newborn born on time. The other significant statistically result of this phase of the study showed that the difference between these four age groups in the NIPEm scores recorded 20 minutes after painful procedure was obvious (p-value=0,032). The younger the newborn were at birth the lower was their NIPEm result. It could indicate that the youngest patients in neonatal intensive care units feel pain more severely with longer nociceptive effects reflecting their level of stress and discomfort too.

The data from researches published up to now had very different results regarding evaluation of acute procedural pain in neonate with the NIPE pain monitor. The study on 29 preterm infants (the range of gestational age 25.1 - 40.8) carried out by Cremillieux et al. assessed induced acute pain. Children's results of the NIPE index, the DAN score and the PIPP-R score did not correlate in this trial and it was concluded that the NIPE index

was not reliable to assess acute pain. One suggestion has been made while evaluating its reliability. The NIPE algorithm calculating heart rate variability of newborns has “smoothing effect of the displayed value over a few tens of seconds” [53] and it could influence the real-time analysis of the painful perception caused by short-lasting noxious stimuli. In my study the minimum NIPEi index that was shown on the monitor within 3 min. of observation was recorded after the procedure. On the display of instantaneous values of NIPE index its declines were detected in the red graph (presented at the photographs of the monitor in the Appendix 1).

The Newborn Infant Parasympathetic evaluation index was also studied for acute procedural pain assessment in preterm infants by Gendras et al. 90 patients of mean gestational age at birth 30.9 were assessed during different painful and stressful interventions and they were evaluated with the PIPP-R scale and the NIPE index. No significant correlation between these two methods of pain evaluation was found. These result where consistent with the study mentioned above again suggesting the NIPE index is not valuable for accurate assessment of acute procedural pain [73].

On the other hand one the results of the research carried out by Walas et al. showed the strong sensitivity and specificity of the NIPE index in detecting acute painful event in nonanesthetized children. 36 infants (postmenstrual age in weeks 28.1 – 48.1) were evaluated with the NIPE monitor during noxious procedure including heel pricks, venipunctures, lumbar punctures and subcutaneous injections. The study also confirmed that the statistically significant decrease in the NIPE index value was observed within 3 minutes after the painful procedure was performed [196].

Another study of the parasympathetic evaluation for procedural pain assessment in neonatology published in 2022 (Carnicero at al.) analyzed changes in the NIPE scores after painful intervention. 49 patients (gestational age in weeks: 31 – 37) were enrolled in that study. The notable decrease of the NIPE index was observed in the first 4 minutes after the procedure. [17]

The NIPE pain monitor was also used in comparison with the Skin Conductance Activity to assess procedural pain in infants without analgosedation (Walas et al.). 33 patients (gestational age at birth 31 – 39 weeks) were evaluated during heel sticks and scored with

the NIPE index and the results of SC presented as Peaks per Second, that were increasing in response to painful stimuli. Patients were also assessed with behavioral scales: the PIPP, the NIPS and the FLACC scale. No statistically significant differences between the NIPEi and the Peaks per Second were detected. It was concluded that the NIPE pain monitor and Skin Conductance activity may be useful for detection of procedural pain [195].

Walas et al. conducted a survey too in the topic of usefulness of two pain monitors in newborns treated in neonatal intensive care units. According to Polish experts the NIPE pain monitor and the SC monitor are useful. The NIPE monitor was assessed a little higher. It was stated that any possible way to improve pain evaluation in newborns is relevant to provide them accurate pain treatment [197].

Okur et. al assessed the neonatal pain with HRV analysis with the Newborn Parasympathetic Evaluation index in newborns treated with surfactant. 14 preterm infants were evaluated while surfactant administration by minimally invasive method or by the INSURE method. Statistically significant difference in median HRV was observed between these two methods suggesting that the minimally invasive technique may be less stressful and painful for preterm newborns.

In the study of pain in neonates that was presented in this doctoral thesis in the second sub-study evaluating the sensitivity of newborns to painful stimuli, factors potentially influencing the NIPE index results were analyzed. The NIPE scores were not affected by gender or the type of procedural pain. On the other hand there was significant difference between age groups. Only one study mentioned above conducted by Carnicero et al. assessed factors like gestational age, gender, repetition of procedures and infant's position in relation to the NIPE values.

While conducting this study and evaluating the pain in neonates one more observation was clear. The use of analgesia in neonatal intensive care unit was and still remains insufficient. Several studies confirmed that gaps between knowledge and practice regarding pain management are visible at NICUs [4, 156, 165, 191]. It is essential to revise actual evidence based guidelines of pain prevention and management. Moreover communication and collaboration among health professionals is crucial to choose the most optimal and safest pain relief strategy for newborns in intensive care units [21, 118].

Every neonatal department should have pain management policy or protocol and members of neonatological team ought to be educated on its use [126, 153].

There is a plethora means to assess pain in neonates, however the individual approach is advised to choose the most suitable scale or monitor. Despite of great advances in neonatology evaluation and management of pain still remains complex issue of newborns medical care. So far limited data on the clinical use of the Newborn Parasympathetic Evaluation Index were published and their results varied. Further investigation of clinical utility of the NIPE pain monitor is suggested to recommend it as a standard pain assessment tool in neonates.

The study of pain in neonates showed clearly that newborns are capable of detecting painful events during their stay at NICUs. Patients should be regularly evaluated during intensive treatment to provide them proper pain relief method – either non-pharmacologically or pharmacologically or with combined ways of analgesia for better results. The inaccurate pain assessment results in inconsistencies and variability in pain treatment. Watchful observation of children in NICUs is the mainstay for improving their individual care and to prevent adverse complications. The constant evaluation of children even as young as 24 gestational week at birth would enable individually tailored pain management according to the NIPE index results.

Every patient's well-being gives the motivation of constant progress in medicine and in neonatology. In the topic of pain in neonates there is still many aspects to be researched.

LIMITATIONS OF THE STUDY

The NIPE index that was used to evaluate newborns in this study may be affected (as well as hear rate variability) by various environmental conditions, drugs and the clinical state of the patients. However the environmental factors of all enrolled patients were strictly controlled and the inclusion criteria were chosen to avoid the bias resulting from patients congenital defects, neurological state or the administrated drugs.

The main limitation of the study of pain was the sample size, although the results of the monitored patients turned out to have clinical practical value and the most important analyzed data were statistically significant.

VIII. CONCLUSIONS

1. The study confirmed that the NIPE pain monitor is valid, reliable and useful tool to evaluate preterm patients experiencing acute prolonged pain and to assess the level of pain during acute noxious procedures in neonates of different gestational age at birth. This device makes pain visible on its display and impossible to deny by health providers. It is easy to interpret and what is very important not observer-independent. Patients can be assessed constantly with the NIPE pain monitor.

2. The results of monitored newborns with the NIPE pain monitor significantly correlated with well-known and extensively researched before pain scales: the Neonatal Pain, Agitation and Sedation Scale (N-PASS), the Premature Infants Pain Profile (PIPP) and the Neonatal Pain and Discomfort Scale (EDIN). The compared results of pain assessment scales and the NIPEm index had very high agreement in the accuracy tests.

3. The results of the NIPE monitoring despite the small number of patients enrolled to the study confirmed that premature infants are more sensitive to pain than full-term newborns. Moreover the findings of the study suggest that the youngest patients in the neonatal intensive care units feel pain more severely with longer nociceptive effects of performed painful procedure.

IX. ABSTRACT

1. INTRODUCTION

The Neonatal Intensive Care Unit is a place that provides live-saving medical care for increasing number of patients each year. Neonates are subjected to numerous painful diagnostic and therapeutic procedures without sufficient analgesia. Early and cumulative pain exposure in newborns at the critical period of their development has been associated with many adverse long-term complications. Therefore the great concern about these consequences gives the motivation to use the best, reliable tools to assess pain in newborns accurately and start the optimal and individually tailored treatment.

2. AIMS OF THE STUDY

The overall aim of the study was to establish the utility of the NIPE pain monitor in different clinical situations and to assess its reliability to monitor pain in newborns.
The objective of the first phase of the study was to compare different methods of pain assessment in preterm neonates experiencing acute prolonged pain: the Newborn Infant Parasympathetic Evaluation (NIPE) index; the Neonatal Pain, Agitation and Sedation Scale (N-PASS); the Premature Infants Pain Profile (PIPP) and the Neonatal Pain and Discomfort Scale (EDIN). The objective of the second part of the study was to evaluate of the level of pain in neonates caused by an acute procedural noxious event and to assess their sensitivity to pain depending on gestational age using the NIPE index.

3. MATERIAL AND METHODS

This was a prospective observational study. It consisted of two phases. In the first part of the study preterm neonates experiencing acute prolonged pain – ventilated newborns were included. In the second experimental group neonates at different gestational age subjected to acute procedural pain were enrolled for the assessment. Exclusion criteria for both phases of the study were: neurological or cardiac congenital anomalies, arrythmias, circulatory failure requiring infusion of vasopressive drugs or fluid resuscitation and severe encephalopathy. The control group consisted of healthy newborns not subjected to any noxious stimuli.

Preterm ventilated infants were evaluated with three behavioral scales: the N-PASS scale, the PIPP scale, the EDIN scale and with the NIPE index. In the second sub-study newborn at different gestational age were assessed with the NIPE pain monitor.

4. RESULTS

40 patients (21 male neonates and 19 female neonates) were included in the study of pain: The analysis of results of the first experimental group of neonates assessed with behavioral scales and with the NIPE pain monitor confirmed that ventilated patients may potentially feel pain. The correlation analysis showed that there is very strong and high significant correlation between the pain scales scores and the NIPEm results. Calculated accuracy confirmed very high agreement between all of the evaluation tools.

Neonates subjected to acute procedural pain were assessed only with the NIPE pain monitor. There was statistically significant difference in the minimum NIPEi results during the evaluation between full term, moderate or late preterm, very preterm and extremely preterm neonates with procedural pain (p-value = 0,033). The decrease of NIPE index was generally higher in neonates born prematurely than in term newborns which would suggest that preterm babies are more sensitive to pain than term-babies. Moreover there was statistically significant difference in the NIPEm scores 20 min. after painful procedures (p-value = 0.032) between different age groups of newborns. It could mean that the youngest children feel pain more severely with longer nociceptive effects of performed painful procedure.

5. CONCLUSIONS

The study proved that the NIPE pain monitor is a reliable tool for pain assessment in preterm newborns experiencing acute prolonged pain and to assess the level of pain caused by acute noxious procedure in neonates. The NIPE results were significantly correlating with the pain assessment scales scores. Additionally study findings confirmed that premature infants are more sensitive to pain that full-term neonates. The NIPE pain monitor has the potential of becoming the gold standard in pain evaluation for newborns born at different gestational week in various clinical situations, nevertheless more research is necessary to conclude that.

KEY WORDS: pain, newborns, pain assessment, pain management

X. REFERENCES

1. Ahn Y. The relationship between behavioral states and pain responses to various NICU procedures in premature infants. J Trop Pediatr. 2006 Jun;52(3):201-5. doi: 10.1093/tropej/fmi099. Epub 2005 Nov 16. PMID: 16291831.
2. Akuma AO, Jordan S. Pain management in neonates: a survey of nurses and doctors. J Adv Nurs. 2012 Jun;68(6):1288-301. doi: 10.1111/j.1365-2648.2011.05837.x. Epub 2011 Oct 11. PMID: 21988718.
3. Allegaert K. A Critical Review on the Relevance of Paracetamol for Procedural Pain Management in Neonates. Front Pediatr. 2020 Mar 18;8:89. doi: 10.3389/fped.2020.00089. PMID: 32257982; PMCID: PMC7093493.
4. Allegaert K, van den Anker JN. Neonatal pain management: still in search for the Holy Grail. Int J Clin Pharmacol Ther. 2016 Jul;54(7):514-23. doi: 10.5414/CP202561. PMID: 27087155; PMCID: PMC5012190.
5. Allegaert K, Tibboel D, van den Anker J. Pharmacological treatment of neonatal pain: in search of a new equipoise. Semin Fetal Neonatal Med. 2013 Feb;18(1):42-7. doi: 10.1016/j.siny.2012.10.001. Epub 2012 Oct 27. PMID: 23107602; PMCID: PMC4709244.
6. American Academy of Pediatrics; Committee on Fetus and Newborn; Canadian Paediatric Society; Fetus and Newborn Committee. Prevention and management of pain in the neonate. An update. Adv Neonatal Care. 2007 Jun;7(3):151-60. doi: 10.1097/01.anc.0000278214.49133.7d. PMID: 17844779.
7. Anand KJS. Defining pain in newborns: need for a uniform taxonomy? Acta Paediatr. 2017 Sep;106(9):1438-1444. doi: 10.1111/apa.13936. Epub 2017 Jul 18. PMID: 28556311; PMCID: PMC5601230.
8. Anand KJS. Discovering Pain in Newborn Infants. Anesthesiology. 2019 Aug;131(2):392-395. doi: 10.1097/ALN.0000000000002810. PMID: 31233407.
9. Anand KJS. Pharmacological approaches to the management of pain in the neonatal intensive care unit. J Perinatol. 2007 May;27 Suppl 1:S4-S11. doi: 10.1038/sj.jp.7211712. PMID: 17453028.

10. Anand KJS, Aranda JV, Berde CB, Buckman S, Capparelli EV, Carlo W, Hummel P, Johnston CC, Lantos J, Tutag-Lehr V, Lynn AM, Maxwell LG, Oberlander TF, Raju TN, Soriano SG, Taddio A, Walco GA. Summary proceedings from the neonatal pain-control group. Pediatrics. 2006 Mar;117(3 Pt 2):S9-S22. doi: 10.1542/peds.2005-0620C. PMID: 16777824.
11. Anand KJS, Eriksson M, Boyle EM, Avila-Alvarez A, Andersen RD, Sarafidis K, Polkki T, Matos C, Lago P, Papadouri T, Attard-Montalto S, Ilmoja ML, Simons S, Tameliene R, van Overmeire B, Berger A, Dobrzanska A, Schroth M, Bergqvist L, Courtois E, Rousseau J, Carbajal R; EUROPAIN survey working group of the NeoOpioid Consortium. Assessment of continuous pain in newborns admitted to NICUs in 18 European countries. Acta Paediatr. 2017 Aug;106(8):1248-1259. doi: 10.1111/apa.13810. Epub 2017 Apr 17. PMID: 28257153.
12. Anand KJS, Roue JM, Rovnaghi CR, Marx W, Bornmann L. Historical roots of pain management in infants: A bibliometric analysis using reference publication year spectroscopy. Paediatr Neonatal Pain. 2020 Jul 27;2(2):22-32. doi: 10.1002/pne2.12035. PMID: 35548591; PMCID: PMC8975229.
13. Anderson DE, Patel AD. Infants born preterm, stress, and neurodevelopment in the neonatal intensive care unit: might music have an impact? Dev Med Child Neurol. 2018 Mar;60(3):256-266. doi: 10.1111/dmcn.13663. Epub 2018 Jan 24. PMID: 29363098.
14. Araujo P, Coelho CA, Oliveira MG, Tufik S, Andersen ML. Neonatal Sleep Restriction Increases Nociceptive Sensitivity in Adolescent Mice. Pain Physician. 2018 Mar;21(2):E137-E148. PMID: 29565956.
15. Arias MC, Guinsburg R. Differences between uni-and multidimensional scales for assessing pain in term newborn infants at the bedside. Clinics (Sao Paulo). 2012 Oct;67(10):1165-70. doi: 10.6061/clinics/2012(10)08. PMID: 23070343; PMCID: PMC3460019.
16. Aylward GP. Neurodevelopmental outcomes of infants born prematurely. J Dev Behav Pediatr. 2005 Dec;26(6):427-40. doi: 10.1097/00004703-200512000-00008. PMID: 16344661.

17. Bachiller Carnicero L, Antoñón Rodríguez M, de la Huerga López A, Martín Ramos S, Morales Luengo F, Marín Urueña SI, Caserío Carbonero S. Parasympathetic evaluation for procedural pain assessment in neonatology. An Pediatr (Engl Ed). 2022 Dec;97(6):390-397. doi: 10.1016/j.anpede.2022.08.013. Epub 2022 Oct 11. PMID: 36241543.
18. Badiee Z, Zandi H, Armanian A, Sadeghnia A, Barekatain B. Premedication with intravenous midazolam for neonatal endotracheal intubation: A double blind randomized controlled trial. J Res Med Sci. 2021 Aug 30;26:57. doi: 10.4103/jrms.JRMS_546_19. PMID: 34729065; PMCID: PMC8506249.
19. Badke CM, Marsillio LE, Weese-Mayer DE, Sanchez-Pinto LN. Autonomic Nervous System Dysfunction in Pediatric Sepsis. Front Pediatr. 2018 Oct 9;6:280. doi: 10.3389/fped.2018.00280. PMID: 30356758; PMCID: PMC6189408.
20. Badr LK, Abdallah B, Hawari M, Sidani S, Kassar M, Nakad P, Breidi J. Determinants of premature infant pain responses to heel sticks. Pediatr Nurs. 2010 May-Jun;36(3):129-36. PMID: 20687304.
21. Balice-Bourgois C, Zumstein-Shaha M, Simonetti GD, Newman CJ. Interprofessional Collaboration and Involvement of Parents in the Management of Painful Procedures in Newborns. Front Pediatr. 2020 Jul 23;8:394. doi: 10.3389/fped.2020.00394. PMID: 32793526; PMCID: PMC7390884.
22. Baxter L, Moultrie F, Fitzgibbon S, Aspbury M, Mansfield R, Bastiani M, Rogers R, Jbabdi S, Duff E, Slater R. Functional and diffusion MRI reveal the neurophysiological basis of neonates' noxious-stimulus evoked brain activity. Nat Commun. 2021 May 12;12(1):2744. doi: 10.1038/s41467-021-22960-0. PMID: 33980860; PMCID: PMC8115252.
23. Bäcke P, Bruschettini M, Blomqvist YT, Olsson E. Interventions for the management of Pain and Sedation in Newborns undergoing Therapeutic hypothermia for hypoxic-ischemic encephalopathy (IPSNUT): protocol of a systematic review. Syst Rev. 2022 May 23;11(1):101. doi: 10.1186/s13643-022-01982-9. PMID: 35606836; PMCID: PMC9128112.
24. Bellieni CV, Buonocore G. Neonatal pain treatment: ethical to be effective. J Perinatol. 2008 Feb;28(2):87-8. doi: 10.1038/sj.jp.7211899. PMID: 18235507.

25. Bellieni CV, Stazzoni G, Tei M, Alagna MG, Iacoponi F, Cornacchione S, Bertrando S, Buonocore G. How painful is a heelprick or a venipuncture in a newborn? J Matern Fetal Neonatal Med. 2016;29(2):202-6. doi: 10.3109/14767058.2014.992334. Epub 2014 Dec 23. PMID: 25534000.
26. Beltramini A, Milojevic K, Pateron D. Pain Assessment in Newborns, Infants, and Children. Pediatr Ann. 2017 Oct 1;46(10):e387-e395. doi: 10.3928/19382359-20170921-03. PMID: 29019634.
27. Bhat BV, Plakkal N. Non-pharmacologic Measures for Pain Relief in Preterm Neonates. Indian Pediatr. 2018 Apr 15;55(4):287-288. PMID: 29726822.
28. van den Bosch GE, Tibboel D, de Graaff JC, El Marroun H, van der Lugt A, White T, van Dijk M. Neonatal Pain, Opioid, and Anesthetic Exposure; What Remains in the Human Brain After the Wheels of Time? Front Pediatr. 2022 May 11;10:825725. doi: 10.3389/fped.2022.825725. PMID: 35633952; PMCID: PMC9132108.
29. Bouza H. The impact of pain in the immature brain. J Matern Fetal Neonatal Med. 2009 Sep;22(9):722-32. doi: 10.3109/14767050902926962. PMID: 19526425.
30. Bresesti I, Vanzù G, Redaelli F, Daniele I, Zuccotti GV, Cerritelli F, Lista G, Fabiano V. New perspective for pain control in neonates: a comparative effectiveness research. J Perinatol. 2021 Sep;41(9):2298-2303. doi: 10.1038/s41372-021-01025-6. Epub 2021 Mar 4. PMID: 33664472.
31. Brummelte S, Grunau RE, Chau V, Poskitt KJ, Brant R, Vinall J, Gover A, Synnes AR, Miller SP. Procedural pain and brain development in premature newborns. Ann Neurol. 2012 Mar;71(3):385-96. doi: 10.1002/ana.22267. Epub 2012 Feb 28. PMID: 22374882; PMCID: PMC3760843.
32. Bucsea O, Pillai Riddell R. Non-pharmacological pain management in the neonatal intensive care unit: Managing neonatal pain without drugs. Semin Fetal Neonatal Med. 2019 Aug;24(4):101017. doi: 10.1016/j.siny.2019.05.009. Epub 2019 Jun 5. Erratum in: Semin Fetal Neonatal Med. 2021 Apr;26(2):101027. PMID: 31326301.
33. Bueno M, Yamada J, Harrison D, Khan S, Ohlsson A, Adams-Webber T, Beyene J, Stevens B. A systematic review and meta-analyses of nonsucrose sweet solutions for pain relief in neonates. Pain Res Manag. 2013 May-Jun;18(3):153-61. doi: 10.1155/2013/956549. PMID: 23748256; PMCID: PMC3673933.

34. Buskila D, Neumann L, Zmora E, Feldman M, Bolotin A, Press J. Pain sensitivity in prematurely born adolescents. Arch Pediatr Adolesc Med. 2003 Nov;157(11):1079-82. doi: 10.1001/archpedi.157.11.1079. PMID: 14609898.
35. Butruille L, De jonckheere J, Marcilly R, Boog C, Bras da Costa S, Rakza T, Storme L, Logier L. Development of a pain monitoring device focused on newborn infant applications: The NeoDoloris project. IRBM. 2015 Vol 36(2): 80-85, doi : 10.1016/j.irbm.2015.01.005.
36. Buyuktiryaki M, Uras N, Okur N, Oncel MY, Simsek GK, Isik SO, Oguz SS. Evaluation of prolonged pain in preterm infants with pneumothorax using heart rate variability analysis and EDIN (Échelle Douleur Inconfort Nouveau-Né, neonatal pain and discomfort scale) scores. Korean J Pediatr. 2018 Oct;61(10):322-326. doi: 10.3345/kjp.2017.05939. Epub 2018 Sep 16. PMID: 30304911; PMCID: PMC6212710.
37. Campbell-Yeo M, Eriksson M, Benoit B. Assessment and Management of Pain in Preterm Infants: A Practice Update. Children (Basel). 2022 Feb 11;9(2):244. doi: 10.3390/children9020244. PMID: 35204964; PMCID: PMC8869922.
38. Campbell-Yeo M, Johnston C, Benoit B, Latimer M, Vincer M, Walker CD, Streiner D, Inglis D, Caddell K. Trial of repeated analgesia with Kangaroo Mother Care (TRAKC Trial). BMC Pediatr. 2013 Nov 9;13:182. doi: 10.1186/1471-2431-13-182. PMID: 24284002; PMCID: PMC3828622.
39. Cannavò L, Perrone S, Marseglia L, Viola V, Di Rosa G, Gitto E. Potential benefits of melatonin to control pain in ventilated preterm newborns: An updated review. Pain Pract. 2022 Feb;22(2):248-254. doi: 10.1111/papr.13069. Epub 2021 Sep 9. PMID: 34431588; PMCID: PMC9293012.
40. Carbajal R, Rousset A, Danan C, Coquery S, Nolent P, Ducrocq S, Saizou C, Lapillonne A, Granier M, Durand P, Lenclen R, Coursol A, Hubert P, de Saint Blanquat L, Boëlle PY, Annequin D, Cimerman P, Anand KJ, Bréart G. Epidemiology and treatment of painful procedures in neonates in intensive care units. JAMA. 2008 Jul 2;300(1):60-70. doi: 10.1001/jama.300.1.60. PMID: 18594041.
41. Cardoso S, Silva MJ, Guimarães H. Autonomic nervous system in newborns: a review based on heart rate variability. Childs Nerv Syst. 2017 Jul;33(7):1053-1063. doi: 10.1007/s00381-017-3436-8. Epub 2017 May 13. PMID: 28501900.

42. Carter BS. Pediatric Palliative Care in Infants and Neonates. Children (Basel). 2018 Feb 7;5(2):21. doi: 10.3390/children5020021. PMID: 29414846; PMCID: PMC5835990.
43. Catai AM, Pastre CM, Godoy MF, Silva ED, Takahashi ACM, Vanderlei LCM. Heart rate variability: are you using it properly? Standardisation checklist of procedures. Braz J Phys Ther. 2020 Mar-Apr;24(2):91-102. doi: 10.1016/j.bjpt.2019.02.006. Epub 2019 Feb 26. PMID: 30852243; PMCID: PMC7082649.
44. Cheng X, Zhu H, Mei L, Luo F, Chen X, Zhao Y, Chen S, Pan Y. Artificial Intelligence Based Pain Assessment Technology in Clinical Application of Real-World Neonatal Blood Sampling. Diagnostics (Basel). 2022 Jul 29;12(8):1831. doi: 10.3390/diagnostics12081831. PMID: 36010186; PMCID: PMC9406884.
45. Chiera M, Cerritelli F, Casini A, Barsotti N, Boschiero D, Cavigioli F, Corti CG, Manzotti A. Heart Rate Variability in the Perinatal Period: A Critical and Conceptual Review. Front Neurosci. 2020 Sep 25;14:561186. doi: 10.3389/fnins.2020.561186. PMID: 33071738; PMCID: PMC7544983.
46. Chrysostomou C, Schulman SR, Herrera Castellanos M, Cofer BE, Mitra S, da Rocha MG, Wisemandle WA, Gramlich L. A phase II/III, multicenter, safety, efficacy, and pharmacokinetic study of dexmedetomidine in preterm and term neonates. J Pediatr. 2014 Feb;164(2):276-82.e1-3. doi: 10.1016/j.jpeds.2013.10.002. Epub 2013 Nov 14. PMID: 24238862.
47. Cignacco E, Hamers JP, Stoffel L, van Lingen RA, Gessler P, McDougall J, Nelle M. The efficacy of non-pharmacological interventions in the management of procedural pain in preterm and term neonates. A systematic literature review. Eur J Pain. 2007 Feb;11(2):139-52. doi: 10.1016/j.ejpain.2006.02.010. Epub 2006 Apr 3. PMID: 16580851.
48. Cobo MM, Hartley C, Gursul D, Andritsou F, van der Vaart M, Schmidt Mellado G, Baxter L, Duff EP, Buckle M, Evans Fry R, Green G, Hoskin A, Rogers R, Adams E, Moultrie F, Slater R. Quantifying noxious-evoked baseline sensitivity in neonates to optimise analgesic trials. Elife. 2021 Apr 13;10:e65266. doi: 10.7554/eLife.65266. PMID: 33847561; PMCID: PMC8087440.

49. Cobo MM, Moultrie F, Hauck AGV, Crankshaw D, Monk V, Hartley C, Evans Fry R, Robinson S, van der Vaart M, Baxter L, Adams E, Poorun R, Bhatt A, Slater R. Multicentre, randomised controlled trial to investigate the effects of parental touch on relieving acute procedural pain in neonates (Petal). BMJ Open. 2022 Jul 19;12(7):e061841. doi: 10.1136/bmjopen-2022-061841. PMID: 36250332; PMCID: PMC9301810.
50. COMMITTEE ON FETUS AND NEWBORN and SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE. Prevention and Management of Procedural Pain in the Neonate: An Update. Pediatrics. 2016 Feb;137(2):e20154271. doi: 10.1542/peds.2015-4271. Epub 2016 Jan 25. PMID: 26810788.
51. Cong X, Wu J, Vittner D, Xu W, Hussain N, Galvin S, Fitzsimons M, McGrath JM, Henderson WA. The impact of cumulative pain/stress on neurobehavioral development of preterm infants in the NICU. Early Hum Dev. 2017 May;108:9-16. doi: 10.1016/j.earlhumdev.2017.03.003. Epub 2017 Mar 23. PMID: 28343092; PMCID: PMC5444300.
52. Costa TMS, Oliveira EDS, Silva BVSD, Melo EBB, Carvalho FO, Duarte FHDS, Dantas RAN, Dantas DV. Massage for pain relief in newborns submitted to puncture: systematic review. Rev Gaucha Enferm. 2022 Nov 28;43(spe):e20220029. English, Portuguese. doi: 10.1590/1983-1447.2022.20220029.en. PMID: 36449833.
53. Cremillieux C, Makhlouf A, Pichot V, Trombert B, Patural H. Objective assessment of induced acute pain in neonatology with the Newborn Infant Parasympathetic Evaluation index. Eur J Pain. 2018 Jul;22(6):1071-1079. doi: 10.1002/ejp.1191. Epub 2018 Mar 24. PMID: 29369446.
54. Dan B. What do we know about pain in neonates? Dev Med Child Neurol. 2020 Nov;62(11):1228. doi: 10.1111/dmcn.14655. PMID: 33015837.
55. Debillon T, Zupan V, Ravault N, Magny JF, Dehan M. Development and initial validation of the EDIN scale, a new tool for assessing prolonged pain in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2001 Jul;85(1):F36-41. doi: 10.1136/fn.85.1.f36. PMID: 11420320; PMCID: PMC1721270.

56. De Jonckheere J, Rakza T, Logier R, Jeanne M, Jounwaz R, Storme L. Heart rate variability analysis for newborn infants prolonged pain assessment. Annu Int Conf IEEE Eng Med Biol Soc. 2011;2011:7747-50. doi: 10.1109/IEMBS.2011.6091909. PMID: 22256134.

57. Desai SA, Nanavati RN, Jasani BB, Kabra N. Comparison of Neonatal Pain, Agitation, and Sedation Scale with Premature Infant Pain Profile for the Assessment of Acute Prolonged Pain in Neonates on Assisted Ventilation: A Prospective Observational Study. Indian J Palliat Care. 2017 Jul-Sep;23(3):287-292. doi: 10.4103/IJPC.IJPC_42_17. PMID: 28827932; PMCID: PMC5545954.

58. Disma N, Veyckemans F, Virag K, Hansen TG, Becke K, Harlet P, Vutskits L, Walker SM, de Graaff JC, Zielinska M, Simic D, Engelhardt T, Habre W; NECTARINE Group of the European Society of Anaesthesiology Clinical Trial Network; Austria; Belgium; Croatia; Czech Republic; Denmark; Estonia; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Latvia; Lithuania; Luxembourg; Malta; Netherlands; Norway; Poland; Portugal; Romania; Serbia; Slovakia; Slovenia; Spain; Switzerland; Turkey; Ukraine; United Kingdom. Morbidity and mortality after anaesthesia in early life: results of the European prospective multicentre observational study, neonate and children audit of anaesthesia practice in Europe (NECTARINE). Br J Anaesth. 2021 Jun;126(6):1157-1172. doi: 10.1016/j.bja.2021.02.016. Epub 2021 Apr 1. PMID: 33812668.

59. Doesburg SM, Chau CM, Cheung TPL, Moiseev A, Ribary U, Herdman AT, Miller SP, Cepeda IL, Synnes A, Grunau RE. Neonatal pain-related stress, functional cortical activity and visual-perceptual abilities in school-age children born at extremely low gestational age. Pain. 2013 Oct;154(10):1946-1952. doi: 10.1016/j.pain.2013.04.009. Epub 2013 Apr 8. PMID: 23711638; PMCID: PMC3778166.

60. Duerden EG, Grunau RE, Guo T, Foong J, Pearson A, Au-Young S, Lavoie R, Chakravarty MM, Chau V, Synnes A, Miller SP. Early Procedural Pain Is Associated with Regionally-Specific Alterations in Thalamic Development in Preterm Neonates. J Neurosci. 2018 Jan 24;38(4):878-886. doi: 10.1523/JNEUROSCI.0867-17.2017. Epub 2017 Dec 18. PMID: 29255007; PMCID: PMC5783966.

61. Durrmeyer X, Vutskits L, Anand KJ, Rimensberger PC. Use of analgesic and sedative drugs in the NICU: integrating clinical trials and laboratory data. Pediatr Res. 2010 Feb;67(2):117-27. doi: 10.1203/PDR.0b013e3181c8eef3. PMID: 20091937.

62. Eerdekens M, Beuter C, Lefeber C, van den Anker J. The challenge of developing pain medications for children: therapeutic needs and future perspectives. J Pain Res. 2019 May 23;12:1649-1664. doi: 10.2147/JPR.S195788. PMID: 31213880; PMCID: PMC6536714.

63. Eiselt M, Curzi-Dascalova L, Clairambault J, Kauffmann F, Médigue C, Peirano P. Heart-rate variability in low-risk prematurely born infants reaching normal term: a comparison with full-term newborns. Early Hum Dev. 1993 Mar;32(2-3):183-95. doi: 10.1016/0378-3782(93)90011-i. PMID: 8486120.

64. Faye PM, De Jonckheere J, Logier R, Kuissi E, Jeanne M, Rakza T, Storme L. Newborn infant pain assessment using heart rate variability analysis. Clin J Pain. 2010 Nov-Dec;26(9):777-82. doi: 10.1097/ajp.0b013e3181ed1058. PMID: 20973153.

65. Filippa M, Monaci MG, Spagnuolo C, Serravalle P, Daniele R, Grandjean D. Maternal speech decreases pain scores and increases oxytocin levels in preterm infants during painful procedures. Sci Rep. 2021 Aug 27;11(1):17301. doi: 10.1038/s41598-021-96840-4. PMID: 34453088; PMCID: PMC8397753.

66. Fitri SYR, Nasution SK, Nurhidayah I, Maryam NNA. Massage therapy as a non-pharmacological analgesia for procedural pain in neonates: A scoping review. Complement Ther Med. 2021 Jun;59:102735. doi: 10.1016/j.ctim.2021.102735. Epub 2021 May 8. PMID: 33974990.

67. Fitzgerald M. What do we really know about newborn infant pain? Exp Physiol. 2015 Dec;100(12):1451-7. doi: 10.1113/EP085134. PMID: 26446174.

68. Francisco ASPG, Montemezzo D, Ribeiro SNDS, Frata B, Menegol NA, Okubo R, Sonza A, Sanada LS. Positioning Effects for Procedural Pain Relief in NICU: Systematic Review. Pain Manag Nurs. 2021 Apr;22(2):121-132. doi: 10.1016/j.pmn.2020.07.006. Epub 2020 Aug 27. PMID: 32863161.

69. Franck LS, Allen A, Cox S, Winter I. Parents' views about infant pain in neonatal intensive care. Clin J Pain. 2005 Mar-Apr;21(2):133-9. doi: 10.1097/00002508-200503000-00004. PMID: 15722806.

70. Fyfe KL, Yiallourou SR, Wong FY, Odoi A, Walker AM, Horne RS. The Effect of Gestational Age at Birth on Post-Term Maturation of Heart Rate Variability. Sleep. 2015 Oct 1;38(10):1635-44. doi: 10.5665/sleep.5064. PMID: 25902805; PMCID: PMC4576338.
71. Garcia-Rodriguez MT, Bujan-Bravo S, Seijo-Bestilleiro R, Gonzalez-Martin C. Pain assessment and management in the newborn: A systematized review. World J Clin Cases. 2021 Jul 26;9(21):5921-5931. doi: 10.12998/wjcc.v9.i21.5921. PMID: 34368310; PMCID: PMC8316969.
72. Garten L, Bührer C. Pain and distress management in palliative neonatal care. Semin Fetal Neonatal Med. 2019 Aug;24(4):101008. doi: 10.1016/j.siny.2019.04.008. Epub 2019 Apr 20. PMID: 31056417.
73. Gendras J, Lavenant P, Sicard-Cras I, Consigny M, Misery L, Anand KJS, Sizun J, Roué JM. The newborn infant parasympathetic evaluation index for acute procedural pain assessment in preterm infants. Pediatr Res. 2021 May;89(7):1840-1847. doi: 10.1038/s41390-020-01152-4. Epub 2020 Sep 22. PMID: 32961546.
74. Gibbins S, Stevens B, Beyene J, Chan PC, Bagg M, Asztalos E. Pain behaviours in Extremely Low Gestational Age infants. Early Hum Dev. 2008 Jul;84(7):451-8. doi: 10.1016/j.earlhumdev.2007.12.007. Epub 2008 Feb 19. PMID: 18243593.
75. Gibbins S, Stevens B, McGrath PJ, Yamada J, Beyene J, Breau L, Camfield C, Finley A, Franck L, Johnston C, Howlett A, McKeever P, O'Brien K, Ohlsson A. Comparison of pain responses in infants of different gestational ages. Neonatology. 2008;93(1):10-8. doi: 10.1159/000105520. Epub 2007 Jul 12. PMID: 17630493.
76. Giordano V, Edobor J, Deindl P, Wildner B, Goeral K, Steinbauer P, Werther T, Berger A, Olischar M. Pain and Sedation Scales for Neonatal and Pediatric Patients in a Preverbal Stage of Development: A Systematic Review. JAMA Pediatr. 2019 Dec 1;173(12):1186-1197. doi: 10.1001/jamapediatrics.2019.3351. PMID: 31609437.
77. Golianu B, Krane E, Seybold J, Almgren C, Anand KJ. Non-pharmacological techniques for pain management in neonates. Semin Perinatol. 2007 Oct;31(5):318-22. doi: 10.1053/j.semperi.2007.07.007. PMID: 17905187.

78. Goto T, Inoue T, Kamiya C, Kawabe H, Higuchi M, Suyama M, Goto T, Koide W, Maki K, Ushijima K, Ban K, Yamada Y. Neonatal pain response to automatic lancet versus needle heel-prick blood sampling: A prospective randomized controlled clinical trial. Pediatr Int. 2020 Mar;62(3):357-362. doi: 10.1111/ped.14142. PMID: 31917874; PMCID: PMC7187310.
79. Goubet N, Clifton RK, Shah B. Learning about pain in preterm newborns. J Dev Behav Pediatr. 2001 Dec;22(6):418-24. doi: 10.1097/00004703-200112000-00009. PMID: 11773806.
80. Green G, Hartley C, Hoskin A, Duff E, Shriver A, Wilkinson D, Adams E, Rogers R, Moultrie F, Slater R. Behavioural discrimination of noxious stimuli in infants is dependent on brain maturation. Pain. 2019 Feb;160(2):493-500. doi: 10.1097/j.pain.0000000000001425. PMID: 30422872; PMCID: PMC6343955.
81. Grunau RE. Neonatal pain in very preterm infants: long-term effects on brain, neurodevelopment and pain reactivity. Rambam Maimonides Med J. 2013 Oct 29;4(4):e0025. doi: 10.5041/RMMJ.10132. PMID: 24228168; PMCID: PMC3820298.
82. Grunau RE, Whitfield MF, Petrie-Thomas J, Synnes AR, Cepeda IL, Keidar A, Rogers M, Mackay M, Hubber-Richard P, Johannesen D. Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants. Pain. 2009 May;143(1-2):138-46. doi: 10.1016/j.pain.2009.02.014. PMID: 19307058; PMCID: PMC2836793.
83. Guedj R, Danan C, Daoud P, Zupan V, Renolleau S, Zana E, Aizenfisz S, Lapillonne A, de Saint Blanquat L, Granier M, Durand P, Castela F, Coursol A, Hubert P, Cimerman P, Anand KJ, Khoshnood B, Carbajal R. Does neonatal pain management in intensive care units differ between night and day? An observational study. BMJ Open. 2014 Feb 20;4(2):e004086. doi: 10.1136/bmjopen-2013-004086. PMID: 24556241; PMCID: PMC3931991.
84. Hall RW. Anesthesia and analgesia in the NICU. Clin Perinatol. 2012 Mar;39(1):239-54. doi: 10.1016/j.clp.2011.12.013. PMID: 22341549; PMCID: PMC3612887.
85. Hall RW, Anand KJ. Pain management in newborns. Clin Perinatol. 2014 Dec;41(4):895-924. doi: 10.1016/j.clp.2014.08.010. Epub 2014 Oct 7. PMID: 25459780; PMCID: PMC4254489.

86. Hammer GB, Maxwell LG, Taicher BM, Visoiu M, Cooper DS, Szmuk P, Pheng LH, Gosselin NH, Lu J, Devarakonda K. Randomized Population Pharmacokinetic Analysis and Safety of Intravenous Acetaminophen for Acute Postoperative Pain in Neonates and Infants. J Clin Pharmacol. 2020 Jan;60(1):16-27. doi: 10.1002/jcph.1508. Epub 2019 Aug 25. PMID: 31448420; PMCID: PMC6973014.
87. Hand IL, Noble L, Geiss D, Wozniak L, Hall C. COVERS Neonatal Pain Scale: Development and Validation. Int J Pediatr. 2010;2010:496719. doi: 10.1155/2010/496719. Epub 2010 Oct 5. PMID: 20976299; PMCID: PMC2952799.
88. Harrison D, Bueno M, Reszel J. Prevention and management of pain and stress in the neonate. Res and Rep in Neonat. 2015;5:9-16. doi: 10.2147/RRN.S52378.
89. Hartley C, Duff EP, Green G, Mellado GS, Worley A, Rogers R, Slater R. Nociceptive brain activity as a measure of analgesic efficacy in infants. Sci Transl Med. 2017 May 3;9(388):eaah6122. doi: 10.1126/scitranslmed.aah6122. PMID: 28469039; PMCID: PMC5884430.
90. Hartley C, Slater R. Neurophysiological measures of nociceptive brain activity in the newborn infant--the next steps. Acta Paediatr. 2014 Mar;103(3):238-42. doi: 10.1111/apa.12490. Epub 2014 Feb 4. PMID: 24180281; PMCID: PMC3992895.
91. Hartley KA, Miller CS, Gephart SM. Facilitated tucking to reduce pain in neonates: evidence for best practice. Adv Neonatal Care. 2015 Jun;15(3):201-8. doi: 10.1097/ANC.0000000000000193. PMID: 26002861.
92. Hatfield LA. Neonatal pain: What's age got to do with it? Surg Neurol Int. 2014 Nov 13;5(Suppl 13):S479-89. doi: 10.4103/2152-7806.144630. PMID: 25506507; PMCID: PMC4253046.
93. Hayano J, Yuda E. Pitfalls of assessment of autonomic function by heart rate variability. J Physiol Anthropol. 2019 Mar 13;38(1):3. doi: 10.1186/s40101-019-0193-2. PMID: 30867063; PMCID: PMC6416928.
94. Holsti L, Grunau RE, Shany E. Assessing pain in preterm infants in the neonatal intensive care unit: moving to a 'brain-oriented' approach. Pain Manag. 2011 Mar 1;1(2):171-179. doi: 10.2217/pmt.10.19. PMID: 21874145; PMCID: PMC3161414.

95. Hsieh KH, Chen SJ, Tsao PC, Wang CC, Huang CF, Lin CM, Chou YL, Chen WY, Chan IC. The analgesic effect of non-pharmacological interventions to reduce procedural pain in preterm neonates. Pediatr Neonatol. 2019 Aug;60(4):481-482. doi: 10.1016/j.pedneo.2019.05.002. Epub 2019 May 16. PMID: 31279689.
96. Huang XZ, Li L, Zhou J, He F, Zhong CX, Wang B. Evaluation of three pain assessment scales used for ventilated neonates. J Clin Nurs. 2018 Oct;27(19-20):3522-3529. doi: 10.1111/jocn.14585. Epub 2018 Jul 27. PMID: 29945293.
97. Hummel P, Puchalski M, Creech SD, Weiss MG. Clinical reliability and validity of the N-PASS: neonatal pain, agitation and sedation scale with prolonged pain. J Perinatol. 2008 Jan;28(1):55-60. doi: 10.1038/sj.jp.7211861. Epub 2007 Oct 25. PMID: 18165830.
98. Ilhan E, Pacey V, Brown L, Spence K, Galea C, Adams R, Hush JM. Exploration and Validation of Behavioral Pain Measures and Physiological Pain Measures Factor Structure Extracted From the Pain Assessment Tool Item Scores for Infants Admitted to Neonatal Intensive Care. Clin J Pain. 2021 Jun 1;37(6):397-403. doi: 10.1097/AJP.0000000000000931. PMID: 33734145.
99. Ilhan E, Pacey V, Brown L, Spence K, van Ganzewinkel CJ, Pillai Riddell R, Campbell-Yeo M, Stevens BJ, Eriksson M, Shah V, Anand KJS, Bellieni C, Daly M, Johnston C, Hush J. What is the definition of acute episodic and chronic pain in critically ill neonates and infants? A global, four-stage consensus and validation study. BMJ Open. 2022 Mar 9;12(3):e055255. doi: 10.1136/bmjopen-2021-055255. PMID: 35264356; PMCID: PMC8915348.
100. Javorka K, Javorka M, Tonhajzerova I, Calkovska A, Lehotska Z, Bukovinska Z, Zibolen M (2011) Determinants of Heart Rate in Newborns. Acta Medica Martiniana. 11(2) 7-16. doi: 10.2478/v10201-011-0012-x.
101. Javorka K, Lehotska Z, Kozar M, Uhrikova Z, Kolarovszki B, Javorka M, Zibolen M. Heart rate variability in newborns. Physiol Res. 2017 Sep 22;66(Suppl 2):S203-S214. doi: 10.33549/physiolres.933676. PMID: 28937235.
102. Johnston C, Campbell-Yeo M, Disher T, Benoit B, Fernandes A, Streiner D, Inglis D, Zee R. Skin-to-skin care for procedural pain in neonates. Cochrane Database Syst Rev. 2017 Feb 16;2(2):CD008435. doi: 10.1002/14651858.CD008435.pub3. PMID: 28205208; PMCID: PMC6464258.

103. Johnston CC, Stevens B. Pain assessment in newborns. J Perinat Neonatal Nurs. 1990 Jul;4(1):41-52. doi: 10.1097/00005237-199007000-00006. PMID: 2192028.
104. Jones L, Laudiano-Dray MP, Whitehead K, Meek J, Fitzgerald M, Fabrizi L, Pillai Riddell R. The impact of parental contact upon cortical noxious-related activity in human neonates. Eur J Pain. 2021 Jan;25(1):149-159. doi: 10.1002/ejp.1656. Epub 2020 Sep 23. PMID: 32965725; PMCID: PMC8436758.
105. Jones L, Laudiano-Dray MP, Whitehead K, Verriotis M, Meek J, Fitzgerald M, Fabrizi L. EEG, behavioural and physiological recordings following a painful procedure in human neonates. Sci Data. 2018 Nov 13;5:180248. doi: 10.1038/sdata.2018.248. PMID: 30422128; PMCID: PMC6233256.
106. Kabra NS, Udani RH. Pain in neonate. Indian J Pediatr. 1999 Jan-Feb;66(1):121-30. doi: 10.1007/BF02752369. PMID: 10798044.
107. Kappesser J, Kamper-Fuhrmann E, de Laffolie J, Faas D, Ehrhardt H, Franck LS, Hermann C. Pain-specific Reactions or Indicators of a General Stress Response?: Investigating the Discriminant Validity of 5 Well-established Neonatal Pain Assessment Tools. Clin J Pain. 2019 Feb;35(2):101-110. doi: 10.1097/AJP.0000000000000660. PMID: 30247197.
108. Karpe J, Misiołek A, Daszkiewicz A, Misiołek H. Objective assessment of pain-related stress in mechanically ventilated newborns based on skin conductance fluctuations. Anaesthesiol Intensive Ther. 2013 Jul-Sep;45(3):134-7. doi: 10.5603/AIT.2013.0028. PMID: 24092508.
109. Kasser S, Hartley C, Rickenbacher H, Klarer N, Depoorter A, Datta AN, Cobo MM, Goksan S, Hoskin A, Magerl W, Huhn EA, Green G, Slater R, Wellmann S. Birth experience in newborn infants is associated with changes in nociceptive sensitivity. Sci Rep. 2019 Mar 11;9(1):4117. doi: 10.1038/s41598-019-40650-2. PMID: 30858561; PMCID: PMC6412011.
110. Kozar M, Tonhajzerova I, Mestanik M, Matasova K, Zibolen M, Calkovska A, Javorka K. Heart rate variability in healthy term newborns is related to delivery mode: a prospective observational study. BMC Pregnancy Childbirth. 2018 Jun 27;18(1):264. doi: 10.1186/s12884-018-1900-4. PMID: 29945544; PMCID: PMC6020381.

111. Krueger C, van Oostrom JH, Shuster J. A longitudinal description of heart rate variability in 28--34-week-old preterm infants. Biol Res Nurs. 2010 Jan;11(3):261-8. doi: 10.1177/1099800409341175. Epub 2009 Nov 23. PMID: 19934110; PMCID: PMC3686561.
112. Kumar P, Denson SE, Mancuso TJ; Committee on Fetus and Newborn, Section on Anesthesiology and Pain Medicine. Premedication for nonemergency endotracheal intubation in the neonate. Pediatrics. 2010 Mar;125(3):608-15. doi: 10.1542/peds.2009-2863. Epub 2010 Feb 22. PMID: 20176672.
113. Kumar P, Sharma R, Rathour S, Karol S, Karol M. Effectiveness of various nonpharmacological analgesic methods in newborns. Clin Exp Pediatr. 2020 Jan;63(1):25-29. doi: 10.3345/kjp.2017.05841. Epub 2019 Aug 16. PMID: 31431605; PMCID: PMC7027346.
114. Labrie NHM. Family reflections: pain in premature infants. Pediatr Res. 2020 Jan;87(1):176-177. doi: 10.1038/s41390-019-0660-9. Epub 2019 Nov 6. PMID: 31694046.
115. Lago P, Garetti E, Merazzi D, Pieragostini L, Ancora G, Pirelli A, Bellieni CV; Pain Study Group of the Italian Society of Neonatology. Guidelines for procedural pain in the newborn. Acta Paediatr. 2009 Jun;98(6):932-9. doi: 10.1111/j.1651-2227.2009.01291.x. PMID: 19484828; PMCID: PMC2688676.
116. Lan HY, Yang L, Lin CH, Hsieh KH, Chang YC, Yin T. Breastmilk as a Multisensory Intervention for Relieving Pain during Newborn Screening Procedures: A Randomized Control Trial. Int J Environ Res Public Health. 2021 Dec 10;18(24):13023. doi: 10.3390/ijerph182413023. PMID: 34948633; PMCID: PMC8701293.
117. Larsson BA. Pain management in neonates. Acta Paediatr. 1999 Dec;88(12):1301-10. doi: 10.1080/080352599750029952. PMID: 10626509.
118. Latimer MA, Johnston CC, Ritchie JA, Clarke SP, Gilin D. Factors affecting delivery of evidence-based procedural pain care in hospitalized neonates. J Obstet Gynecol Neonatal Nurs. 2009 Mar-Apr;38(2):182-94. doi: 10.1111/j.1552-6909.2009.01007.x. PMID: 19323714; PMCID: PMC2756600.

119. Latremouille S, Al-Jabri A, Lamer P, Kanbar L, Shalish W, Kearney RE, Sant'Anna GM. Heart Rate Variability in Extremely Preterm Infants Receiving Nasal CPAP and Non-Synchronized Noninvasive Ventilation Immediately After Extubation. Respir Care. 2018 Jan;63(1):62-69. doi: 10.4187/respcare.05672. Epub 2017 Oct 24. PMID: 29066587.
120. Latremouille S, Lam J, Shalish W, Sant'Anna G. Neonatal heart rate variability: a contemporary scoping review of analysis methods and clinical applications. BMJ Open. 2021 Dec 21;11(12):e055209. doi: 10.1136/bmjopen-2021-055209. PMID: 34933863; PMCID: PMC8710426.
121. Lee GY, Yamada J, Kyololo O, Shorkey A, Stevens B. Pediatric clinical practice guidelines for acute procedural pain: a systematic review. Pediatrics. 2014 Mar;133(3):500-15. doi: 10.1542/peds.2013-2744. Epub 2014 Feb 2. PMID: 24488733.
122. Li Q, Tan X, Li X, Tang W, Mei L, Cheng G, Zou Y. Efficacy and safety of combined oral sucrose and nonnutritive sucking in pain management for infants: A systematic review and meta-analysis. PLoS One. 2022 May 6;17(5):e0268033. doi: 10.1371/journal.pone.0268033. PMID: 35522649; PMCID: PMC9075656.
123. Lind J. The infant cry. Proc R Soc Med. 1971 May;64(5):468. PMID: 5576897; PMCID: PMC1812538.
124. Longin E, Gerstner T, Schaible T, Lenz T, König S. Maturation of the autonomic nervous system: differences in heart rate variability in premature vs. term infants. J Perinat Med. 2006;34(4):303-8. doi: 10.1515/JPM.2006.058. PMID: 16856820.
125. Luciana M. Cognitive development in children born preterm: implications for theories of brain plasticity following early injury. Dev Psychopathol. 2003 Fall;15(4):1017-47. doi: 10.1017/s095457940300049x. PMID: 14984136.
126. Lyngstad LT, Steinnes S, Le Marechal F. Improving pain management in a neonatal intensive care unit with single-family room - A quality improvement project. Paediatr Neonatal Pain. 2022 Feb 25;4(2):69-77. doi: 10.1002/pne2.12075. PMID: 35719218; PMCID: PMC9189914.
127. Maciel HIA, Costa MF, Costa ACL, Marcatto JO, Manzo BF, Bueno M. Pharmacological and nonpharmacological measures of pain management and treatment among neonates. Rev Bras Ter Intensiva. 2019;31(1):21-26. doi: 10.5935/0103-507X.20190007. Epub 2019 Mar 21. PMID: 30916233; PMCID: PMC6443311.

128. Macko J, Moravcikova D, Kantor L, Kotikova M, Humpolicek P. Skin conductance as a marker of pain in infants of different gestational age. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2014 Dec;158(4):591-5. doi: 10.5507/bp.2013.066. Epub 2013 Oct 2. PMID: 24089027.
129. Malliani A, Lombardi F, Pagani M. Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. Br Heart J. 1994 Jan;71(1):1-2. doi: 10.1136/hrt.71.1.1. PMID: 8297682; PMCID: PMC483598.
130. Mangat AK, Oei JL, Chen K, Quah-Smith I, Schmölzer GM. A Review of Non-Pharmacological Treatments for Pain Management in Newborn Infants. Children (Basel). 2018 Sep 20;5(10):130. doi: 10.3390/children5100130. PMID: 30241352; PMCID: PMC6210323.
131. Marchal A, Melchior M, Dufour A, Poisbeau P, Zores C, Kuhn P. Pain Behavioural Response to Acoustic and Light Environmental Changes in Very Preterm Infants. Children (Basel). 2021 Nov 24;8(12):1081. doi: 10.3390/children8121081. PMID: 34943277; PMCID: PMC8700556.
132. Mathew PJ, Mathew JL. Assessment and management of pain in infants. Postgrad Med J. 2003 Aug;79(934):438-43. doi: 10.1136/pmj.79.934.438. PMID: 12954954; PMCID: PMC1742785.
133. Maxwell LG, Fraga MV, Malavolta CP. Assessment of Pain in the Newborn: An Update. Clin Perinatol. 2019 Dec;46(4):693-707. doi: 10.1016/j.clp.2019.08.005. Epub 2019 Aug 19. PMID: 31653303.
134. McNair C, Campbell-Yeo M, Johnston C, Taddio A. Nonpharmacologic Management of Pain During Common Needle Puncture Procedures in Infants: Current Research Evidence and Practical Considerations: An Update. Clin Perinatol. 2019 Dec;46(4):709-730. doi: 10.1016/j.clp.2019.08.006. Epub 2019 Aug 26. Erratum in: Clin Perinatol. 2020 Mar;47(1):xv. PMID: 31653304.
135. McPherson C, Miller SP, El-Dib M, Massaro AN, Inder TE. The influence of pain, agitation, and their management on the immature brain. Pediatr Res. 2020 Aug;88(2):168-175. doi: 10.1038/s41390-019-0744-6. Epub 2020 Jan 2. PMID: 31896130; PMCID: PMC7223850.

136. McPherson C, Ortinau CM, Vesoulis Z. Practical approaches to sedation and analgesia in the newborn. J Perinatol. 2021 Mar;41(3):383-395. doi: 10.1038/s41372-020-00878-7. Epub 2020 Nov 29. PMID: 33250515; PMCID: PMC7700106.
137. Meesters N, Dilles T, Simons S, van Dijk M. Do Pain Measurement Instruments Detect the Effect of Pain-Reducing Interventions in Neonates? A Systematic Review on Responsiveness. J Pain. 2019 Jul;20(7):760-770. doi: 10.1016/j.jpain.2018.12.005. Epub 2018 Dec 23. PMID: 30586622.
138. Melo GM, Cardoso MVLML, Almeida PC, Rodrigues EC. Effect of music combined with swaddling on pain in full-term newborns: randomized clinical trial. Rev Bras Enferm. 2021 Oct 25;75(3):e20210017. doi: 10.1590/0034-7167-2021-0017. PMID: 34706047.
139. de Melo GM, Lélis AL, de Moura AF, Cardoso MV, da Silva VM. Escalas de avaliação de dor em recém-nascidos: revisão integrativa [Pain assessment scales in newborns: integrative review]. Rev Paul Pediatr. 2014 Dec;32(4):395-402. doi: 10.1016/j.rpped.2014.04.007. PMID: 25511005; PMCID: PMC4311795.
140. Mencía S, Alonso C, Pallás-Alonso C, López-Herce J, Maternal And Child Health And Development Network Ii Samid Ii. Evaluation and Treatment of Pain in Fetuses, Neonates and Children. Children (Basel). 2022 Nov 3;9(11):1688. doi: 10.3390/children9111688. PMID: 36360416; PMCID: PMC9689143.
141. Mitchell A, Brooks S, Roane D. The premature infant and painful procedures. Pain Manag Nurs. 2000 Jun;1(2):58-65. doi: 10.1053/jpmn.2000.7781. PMID: 11706460.
142. Morgan ME, Kukora S, Nemshak M, Shuman CJ. Neonatal Pain, Agitation, and Sedation Scale's use, reliability, and validity: a systematic review. J Perinatol. 2020 Dec;40(12):1753-1763. doi: 10.1038/s41372-020-00840-7. Epub 2020 Oct 2. PMID: 33009491.
143. Munsters J, Wallström L, Agren J, Norsted T, Sindelar R. Skin conductance measurements as pain assessment in newborn infants born at 22-27 weeks gestational age at different postnatal age. Early Hum Dev. 2012 Jan;88(1):21-6. doi: 10.1016/j.earlhumdev.2011.06.010. Epub 2011 Jul 20. PMID: 21764228.

144. Napiórkowska-Orkisz M, Gutysz-Wojnicka A, Tanajewska M, Sadowska-Krawczenko I. Evaluation of Methods to Minimize Pain in Newborns during Capillary Blood Sampling for Screening: A Randomized Clinical Trial. Int J Environ Res Public Health. 2022 Jan 13;19(2):870. doi: 10.3390/ijerph19020870. PMID: 35055694; PMCID: PMC8775482.
145. Núñez-López I, Collados-Gómez L, Abalo R, Martínez-Pérez P, Moreno-Vicente Á, Cid-Expósito MG. Cultural Adaptation and Validation of the Premature Infant Pain Profile-Revised (PIPP-R) Pain Measurement Scale: Research Protocol. Int J Environ Res Public Health. 2022 Sep 28;19(19):12338. doi: 10.3390/ijerph191912338. PMID: 36231638; PMCID: PMC9566023.
146. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for prevention or treatment of pain in newborns. Cochrane Database Syst Rev. 2020 Jan 27;1(1):CD011219. doi: 10.1002/14651858.CD011219.pub4. PMID: 31985830; PMCID: PMC6984663.
147. Ojha S, Abramson J, Dorling J. Sedation and analgesia from prolonged pain and stress during mechanical ventilation in preterm infants: is dexmedetomidine an alternative to current practice? BMJ Paediatr Open. 2022 May;6(1):e001460. doi: 10.1136/bmjpo-2022-001460. PMID: 36053596; PMCID: PMC9092181.
148. Okur N, Uras N, Buyuktiryaki M, Oncel MY, Saria FN, Yarci E, Dizdar EA, Canpolat FE, Oguz SS. Neonatal pain and heart rate variability in preterm infants treated with surfactant: a pilot study. Arch Argent Pediatr. 2019 Dec 1;117(6):397. English, Spanish. doi: 10.5546/aap.2019.eng.397. PMID: 31758887.
149. Oliveira V, Martins R, Liow N, Teiserskas J, von Rosenberg W, Adjei T, Shivamurthappa V, Lally PJ, Mandic D, Thayyil S. Prognostic Accuracy of Heart Rate Variability Analysis in Neonatal Encephalopathy: A Systematic Review. Neonatology. 2019;115(1):59-67. doi: 10.1159/000493002. Epub 2018 Oct 9. PMID: 30300885.
150. Olsson E, Ahl H, Bengtsson K, Vejayaram DN, Norman E, Bruschettini M, Eriksson M. The use and reporting of neonatal pain scales: a systematic review of randomized trials. Pain. 2021 Feb 1;162(2):353-360. doi: 10.1097/j.pain.0000000000002046. PMID: 32826760; PMCID: PMC7808360.

151. Perroteau A, Nanquette MC, Rousseau A, Renolleau S, Bérard L, Mitanchez D, Leblanc J. Efficacy of facilitated tucking combined with non-nutritive sucking on very preterm infants' pain during the heel-stick procedure: A randomized controlled trial. Int J Nurs Stud. 2018 Oct;86:29-35. doi: 10.1016/j.ijnurstu.2018.06.007. Epub 2018 Jun 15. PMID: 29960105.

152. Perry M, Tan Z, Chen J, Weidig T, Xu W, Cong XS. Neonatal Pain: Perceptions and Current Practice. Crit Care Nurs Clin North Am. 2018 Dec;30(4):549-561. doi: 10.1016/j.cnc.2018.07.013. PMID: 30447813; PMCID: PMC6570422.

153. Peterson J, den Boer MC, Roehr CC. To Sedate or Not to Sedate for Less Invasive Surfactant Administration: An Ethical Approach. Neonatology. 2021;118(6):639-646. doi: 10.1159/000519283. Epub 2021 Oct 8. PMID: 34628413.

154. Pichot V, Roche F, Celle S, Barthélémy JC, Chouchou F. HRVanalysis: A Free Software for Analyzing Cardiac Autonomic Activity. Front Physiol. 2016 Nov 22;7:557. doi: 10.3389/fphys.2016.00557. PMID: 27920726; PMCID: PMC5118625.

155. Popowicz H, Kwiecień-Jaguś K, Olszewska J, Mędrzycka-Dąbrowska WA. Pain Scales in Neonates Receiving Mechanical Ventilation in Neonatal Intensive Care Units - Systematic Review. J Pain Res. 2020 Jul 24;13:1883-1897. doi: 10.2147/JPR.S248042. PMID: 32801846; PMCID: PMC7399469.

156. Prestes AC, Balda Rde C, Santos GM, Rugolo LM, Bentlin MR, Magalhães M, Pachi PR, Marba ST, Caldas JP, Guinsburg R. Painful procedures and analgesia in the NICU: what has changed in the medical perception and practice in a ten-year period? J Pediatr (Rio J). 2016 Jan-Feb;92(1):88-95. doi: 10.1016/j.jped.2015.04.009. Epub 2015 Oct 9. PMID: 26453514.

157. Raffaeli G, Cristofori G, Befani B, De Carli A, Cavallaro G, Fumagalli M, Plevani L, Mosca F. EDIN Scale Implemented by Gestational Age for Pain Assessment in Preterms: A Prospective Study. Biomed Res Int. 2017;2017:9253710. doi: 10.1155/2017/9253710. Epub 2017 Feb 8. PMID: 28271074; PMCID: PMC5320371.

158. Ranger M, Grunau RE. Early repetitive pain in preterm infants in relation to the developing brain. Pain Manag. 2014 Jan;4(1):57-67. doi: 10.2217/pmt.13.61. PMID: 24641344; PMCID: PMC3975052.

159. van Ravenswaaij-Arts CM, Hopman JC, Kollée LA, van Amen JP, Stoelinga GB, van Geijn HP. Influences on heart rate variability in spontaneously breathing preterm infants. Early Hum Dev. 1991 Dec;27(3):187-205. doi: 10.1016/0378-3782(91)90194-8. PMID: 1802671.
160. van Ravenswaaij-Arts CM, Hopman JC, Kollée LA, van Amen JP, Stoelinga GB, van Geijn HP. The influence of respiratory distress syndrome on heart rate variability in very preterm infants. Early Hum Dev. 1991 Dec;27(3):207-21. doi: 10.1016/0378-3782(91)90195-9. PMID: 1802672.
161. van Ravenswaaij-Arts CM, Hopman JC, Kollée LA, Stoelinga GB, van Geijn HP. Spectral analysis of heart rate variability in spontaneously breathing very preterm infants. Acta Paediatr. 1994 May;83(5):473-80. doi: 10.1111/j.1651-2227.1994.tb13062.x. PMID: 8086722.
162. van Ravenswaaij-Arts CM, Hopman JC, Kollée LA, Stoelinga GB, van Geijn HP. The influence of artificial ventilation on heart rate variability in very preterm infants. Pediatr Res. 1995 Jan;37(1):124-30. doi: 10.1203/00006450-199501000-00023. PMID: 7700727.
163. van Ravenswaaij-Arts CM, Kollée LA, Hopman JC, Stoelinga GB, van Geijn HP. Heart rate variability. Ann Intern Med. 1993 Mar 15;118(6):436-47. doi: 10.7326/0003-4819-118-6-199303150-00008. PMID: 8439119.
164. Relland LM, Gehred A, Maitre NL. Behavioral and Physiological Signs for Pain Assessment in Preterm and Term Neonates During a Nociception-Specific Response: A Systematic Review. Pediatr Neurol. 2019 Jan;90:13-23. doi: 10.1016/j.pediatrneurol.2018.10.001. Epub 2018 Oct 10. PMID: 30449602.
165. Rocha VA, Silva IA, da Silveira Cruz-Machado S, Bueno M. Painful procedures and pain management in newborns admitted to an intensive care unit. Rev Esc Enferm USP. 2021 Oct 29;55:e20210232. English, Portuguese. doi: 10.1590/1980-220X-REEUSP-2021-0232. PMID: 34714319.
166. Romantsik O, Calevo MG, Norman E, Bruschettini M. Clonidine for pain in non-ventilated infants. Cochrane Database Syst Rev. 2020 Apr 9;4(4):CD013104. doi: 10.1002/14651858.CD013104.pub2. PMID: 32270873; PMCID: PMC7143321.

167. Roué JM, Rioualen S, Gendras J, Misery L, Gouillou M, Sizun J. Multi-modal pain assessment: are near-infrared spectroscopy, skin conductance, salivary cortisol, physiologic parameters, and Neonatal Facial Coding System interrelated during venepuncture in healthy, term neonates? J Pain Res. 2018 Oct 11;11:2257-2267. doi: 10.2147/JPR.S165810. PMID: 30349352; PMCID: PMC6188070.
168. Saeidi R, Asnaashari Z, Amirnejad M, Esmaeili H, Robatsangi MG. Use of "kangaroo care" to alleviate the intensity of vaccination pain in newborns. Iran J Pediatr. 2011 Mar;21(1):99-102. PMID: 23056772; PMCID: PMC3446105.
169. Salekin MS, Mouton PR, Zamzmi G, Patel R, Goldgof D, Kneusel M, Elkins SL, Murray E, Coughlin ME, Maguire D, Ho T, Sun Y. Future roles of artificial intelligence in early pain management of newborns. Paediatr Neonatal Pain. 2021 Aug 5;3(3):134-145. doi: 10.1002/pne2.12060. PMID: 35547946; PMCID: PMC8975206.
170. Sarkaria E, Gruszfeld D. Assessing Neonatal Pain with NIPS and COMFORT-B: Evaluation of NICU's Staff Competences. Pain Res Manag. 2022 Mar 16;2022:8545372. doi: 10.1155/2022/8545372. PMID: 35340544; PMCID: PMC8942671.
171. Schenk K, Stoffel L, Bürgin R, Stevens B, Bassler D, Schulzke S, Nelle M, Cignacco E. The influence of gestational age in the psychometric testing of the Bernese Pain Scale for Neonates. BMC Pediatr. 2019 Jan 15;19(1):20. doi: 10.1186/s12887-018-1380-8. PMID: 30646872; PMCID: PMC6334397.
172. Schiavenato M, Butler-O'Hara M, Scovanner P. Exploring the association between pain intensity and facial display in term newborns. Pain Res Manag. 2011 Jan-Feb;16(1):10-2. doi: 10.1155/2011/873103. PMID: 21369535; PMCID: PMC3052401.
173. Schiller RM, Allegaert K, Hunfeld M, van den Bosch GE, van den Anker J, Tibboel D. Analgesics and Sedatives in Critically Ill Newborns and Infants: The Impact on Long-Term Neurodevelopment. J Clin Pharmacol. 2018 Oct;58 Suppl 10:S140-S150. doi: 10.1002/jcph.1139. PMID: 30248203.
174. Selig FA, Tonolli ER, Silva EV, Godoy MF. Heart rate variability in preterm and term neonates. Arq Bras Cardiol. 2011 Jun;96(6):443-9. English, Portuguese, Spanish. doi: 10.1590/s0066-782x2011005000059. Epub 2011 May 13. PMID: 21584479.

175. Sellas MN, Kyllonen KC, Lepak MR, Rodriguez RJ. Dexmedetomidine for the Management of Postoperative Pain and Sedation in Newborns. J Pediatr Pharmacol Ther. 2019 May-Jun;24(3):227-233. doi: 10.5863/1551-6776-24.3.227. PMID: 31093022; PMCID: PMC6510519.
176. Shaw SC, Sankar MJ, Thukral A, Agarwal R, Deorari AK, Paul VK. Assisted Physical Exercise and Stress in Preterm Neonates. Indian Pediatr. 2018 Aug 15;55(8):679-682. PMID: 30218515.
177. Shukla VV, Bansal S, Nimbalkar A, Chapla A, Phatak A, Patel D, Nimbalkar S. Pain Control Interventions in Preterm Neonates: A Randomized Controlled Trial. Indian Pediatr. 2018 Apr 15;55(4):292-296. Epub 2018 Feb 9. PMID: 29428919.
178. Sposito NPB, Rossato LM, Bueno M, Kimura AF, Costa T, Guedes DMB. Assessment and management of pain in newborns hospitalized in a Neonatal Intensive Care Unit: a cross-sectional study. Rev Lat Am Enfermagem. 2017 Sep 12;25:e2931. doi: 10.1590/1518-8345.1665.2931. PMID: 28902934; PMCID: PMC5599073.
179. Squillaro A, Mahdi EM, Tran N, Lakshmanan A, Kim E, Kelley-Quon LI. Managing Procedural Pain in the Neonate Using an Opioid-sparing Approach. Clin Ther. 2019 Sep;41(9):1701-1713. doi: 10.1016/j.clinthera.2019.07.014. Epub 2019 Aug 17. PMID: 31431300; PMCID: PMC6790974.
180. Stevens B. Revisions to the IASP definition of pain-What does this mean for children? Paediatr Neonatal Pain. 2021 Mar 27;3(3):101-105. doi: 10.1002/pne2.12047. PMID: 35547949; PMCID: PMC8975187.
181. Stevens B, Johnston C, Petryshen P, Taddio A. Premature Infant Pain Profile: development and initial validation. Clin J Pain. 1996 Mar;12(1):13-22. doi: 10.1097/00002508-199603000-00004. PMID: 8722730.
182. Stevens B, Johnston C, Taddio A, Gibbins S, Yamada J. The premature infant pain profile: evaluation 13 years after development. Clin J Pain. 2010 Nov-Dec;26(9):813-30. doi: 10.1097/AJP.0b013e3181ed1070. PMID: 20717010.
183. Stevens B, McGrath P, Ballantyne M, Yamada J, Dupuis A, Gibbins S, Franck L, Allen Finley G, Howlett A, Johnston C, O'Brien K, Ohlsson A. Influence of risk of neurological impairment and procedure invasiveness on health professionals' management of procedural pain in neonates. Eur J Pain. 2010 Aug;14(7):735-41. doi: 10.1016/j.ejpain.2009.11.016. Epub 2010 Jan 4. PMID: 20047845.

184. Stevens B, Yamada J, Campbell-Yeo M, Gibbins S, Harrison D, Dionne K, Taddio A, McNair C, Willan A, Ballantyne M, Widger K, Sidani S, Estabrooks C, Synnes A, Squires J, Victor C, Riahi S. The minimally effective dose of sucrose for procedural pain relief in neonates: a randomized controlled trial. BMC Pediatr. 2018 Feb 23;18(1):85. doi: 10.1186/s12887-018-1026-x. PMID: 29475433; PMCID: PMC5824554.
185. Stevens BJ, Franck LS. Assessment and management of pain in neonates. Paediatr Drugs. 2001;3(7):539-58. doi: 10.2165/00128072-200103070-00004. PMID: 11513283.
186. Stevens BJ, Franck L. Special needs of preterm infants in the management of pain and discomfort. J Obstet Gynecol Neonatal Nurs. 1995 Nov-Dec;24(9):856-62. doi: 10.1111/j.1552-6909.1995.tb02571.x. PMID: 8583277.
187. Stevens BJ, Johnston CC, Horton L. Factors that influence the behavioral pain responses of premature infants. Pain. 1994 Oct;59(1):101-109. doi: 10.1016/0304-3959(94)90053-1. PMID: 7854790.
188. Subramaniam R. Anaesthetic concerns in preterm and term neonates. Indian J Anaesth. 2019 Sep;63(9):771-779. doi: 10.4103/ija.IJA_591_19. PMID: 31571691; PMCID: PMC6761779.
189. Tannous Elias LS, Dos Santos AM, Guinsburg R. Perception of pain and distress in intubated and mechanically ventilated newborn infants by parents and health professionals. BMC Pediatr. 2014 Feb 15;14:44. doi: 10.1186/1471-2431-14-44. PMID: 24528475; PMCID: PMC3928585.
190. Tesoro S, Marchesini V, Fratini G, Engelhardt T, De Robertis E. Drugs for anesthesia and analgesia in the preterm infant. Minerva Anestesiol. 2020 Jul;86(7):742-755. doi: 10.23736/S0375-9393.20.14073-2. Epub 2020 Jan 28. PMID: 32000473.
191. Thacker JP, Shah DS, Patel DV, Nimbalkar SM. Practices of Procedural Pain Management in Neonates through Continuous Quality Improvement Measures. Int J Pediatr. 2022 Feb 13;2022:8605071. doi: 10.1155/2022/8605071. PMID: 35198029; PMCID: PMC8858718.
192. Thigpen JC, Odle BL, Harirforoosh S. Opioids: A Review of Pharmacokinetics and Pharmacodynamics in Neonates, Infants, and Children. Eur J Drug Metab Pharmacokinet. 2019 Oct;44(5):591-609. doi: 10.1007/s13318-019-00552-0. PMID: 31006834.

193. Thill B. Fetal Pain in the First Trimester. Linacre Q. 2022 Feb;89(1):73-100. doi: 10.1177/00243639211059245. Epub 2021 Dec 6. PMID: 35321491; PMCID: PMC8935428.

194. Walas W, Halaba Z, Kubiaczyk A, Piotrowski A, Latka-Grot J, Szczapa T, Romul M, Maroszyńska I, Malinowska E, Rutkowska M, Skrzypek M, Śmigiel R. Skin conductance measurement for the assessment of analgosedation adequacy in infants treated with mechanical ventilation: A multicenter pilot study. Adv Clin Exp Med. 2020 Sep;29(9):1117-1121. doi: 10.17219/acem/126286. PMID: 32937040.

195. Walas W, Halaba ZP, Szczapa T, Latka-Grot J, Maroszyńska I, Malinowska E, Rutkowska M, Kubiaczyk A, Wrońska M, Skrzypek M, De Jonckheere J, Jean-Noel M, Piotrowski A. Procedural Pain Assessment in Infants Without Analgosedation: Comparison of Newborn Infant Parasympathetic Evaluation and Skin Conductance Activity - A Pilot Study. Front Pediatr. 2022 Jan 11;9:746504. doi: 10.3389/fped.2021.746504. PMID: 35087770; PMCID: PMC8787338.

196. Walas W, Latka-Grot J, Maroszyńska I, Malinowska E, Rutkowska M, Piotrowski A, Wrońska M, Szczapa T, Kubiaczyk A, Skrzypek M, De Jonckheere J, Halaba ZP. Newborn Infant Parasympathetic Evaluation Index for the Assessment of Procedural Pain in Nonanesthetized Infants: A Multicenter Pilot Study. Am J Perinatol. 2021 Aug;38(S 01):e224-e230. doi: 10.1055/s-0040-1709458. Epub 2020 Apr 10. PMID: 32276281.

197. Walas W, Latka-Grot J, Szczapa T, Maroszyńska I, Rutkowska M, Bartkowska-Śniatkowska A, Piotrowski A. Usefulness of two types of pain monitors in newborns treated in NICU, in the opinion of experts: Results of the survey. J Mother Child. 2022 Apr 1;25(2):72-76. doi: 10.34763/jmotherandchild.20212502.d-21-00018. PMID: 34842396; PMCID: PMC8976587.

198. Walas W, Malinowska E, Halaba ZP, Szczapa T, Latka-Grot J, Rutkowska M, Kubiaczyk A, Wrońska M, Piotrowski A, Skrzypek M, Jean-Noel M, Maroszyńska I. Newborn infant parasympathetic evaluation for the assessment of analgosedation adequacy in infants treated by mechanical ventilation - a multicenter pilot study. Arch Med Sci. 2021 Mar 24;17(6):1651-1656. doi: 10.5114/aoms/134234. PMID: 34900045; PMCID: PMC8641521.

199. Walker SM. Long-term effects of neonatal pain. Semin Fetal Neonatal Med. 2019 Aug;24(4):101005. doi: 10.1016/j.siny.2019.04.005. Epub 2019 Apr 5. PMID: 30987942.

200. Walker SM, Melbourne A, O'Reilly H, Beckmann J, Eaton-Rosen Z, Ourselin S, Marlow N. Somatosensory function and pain in extremely preterm young adults from the UK EPICure cohort: sex-dependent differences and impact of neonatal surgery. Br J Anaesth. 2018 Sep;121(3):623-635. doi: 10.1016/j.bja.2018.03.035. Epub 2018 Jun 19. PMID: 30115261; PMCID: PMC6200114.

201. Walker SM, O'Reilly H, Beckmann J, Marlow N; EPICure@19 Study Group. Conditioned pain modulation identifies altered sensitivity in extremely preterm young adult males and females. Br J Anaesth. 2018 Sep;121(3):636-646. doi: 10.1016/j.bja.2018.05.066. Epub 2018 Jul 6. PMID: 30115262; PMCID: PMC6200113.

202. Weiss C. Does circumcision of the newborn require an anesthetic? Clin Pediatr (Phila). 1968 Mar;7(3):128-9. doi: 10.1177/000992286800700302. PMID: 4868474.

203. Weissman A, Zimmer EZ, Aranovitch M, Blazer S. Heart rate dynamics during acute pain in newborns. Pflugers Arch. 2012 Dec;464(6):593-9. doi: 10.1007/s00424-012-1168-x. Epub 2012 Oct 9. PMID: 23053480.

204. Witt N, Coynor S, Edwards C, Bradshaw H. A Guide to Pain Assessment and Management in the Neonate. Curr Emerg Hosp Med Rep. 2016;4:1-10. doi: 10.1007/s40138-016-0089-y. Epub 2016 Mar 12. PMID: 27073748; PMCID: PMC4819510.

205. Wu H, Zhang J, Ding Q, Wang S, Li J. Effect analysis of embracing breast milk sucking to relieve pain of neonatal heel blood sampling: a randomized controlled trial. Ann Palliat Med. 2021 Apr;10(4):4384-4390. doi: 10.21037/apm-21-329. PMID: 33966439.

206. Valeri BO, Holsti L, Linhares MB. Neonatal pain and developmental outcomes in children born preterm: a systematic review. Clin J Pain. 2015 Apr;31(4):355-62. doi: 10.1097/AJP.0000000000000114. PMID: 24866853.

207. Vederhus BJ, Eide GE, Natvig GK, Markestad T, Graue M, Halvorsen T. Pain tolerance and pain perception in adolescents born extremely preterm. J Pain. 2012 Oct;13(10):978-87. doi: 10.1016/j.jpain.2012.07.008. PMID: 23031397.

208. Verweij LM, Kivits JTS, Weber F. The performance of the heart rate variability-derived Newborn Infant Parasympathetic Evaluation Index as a measure of early postoperative pain and discomfort in infants-A prospective observational study. Paediatr Anaesth. 2021 Jul;31(7):787-793. doi: 10.1111/pan.14188. Epub 2021 May 6. PMID: 33811710; PMCID: PMC8251861.
209. Vinall J, Grunau RE. Impact of repeated procedural pain-related stress in infants born very preterm. Pediatr Res. 2014 May;75(5):584-7. doi: 10.1038/pr.2014.16. Epub 2014 Feb 5. PMID: 24500615; PMCID: PMC3992189.
210. Vinall J, Miller SP, Bjornson BH, Fitzpatrick KP, Poskitt KJ, Brant R, Synnes AR, Cepeda IL, Grunau RE. Invasive procedures in preterm children: brain and cognitive development at school age. Pediatrics. 2014 Mar;133(3):412-21. doi: 10.1542/peds.2013-1863. Epub 2014 Feb 17. PMID: 24534406; PMCID: PMC3934331.
211. Vinall J, Miller SP, Chau V, Brummelte S, Synnes AR, Grunau RE. Neonatal pain in relation to postnatal growth in infants born very preterm. Pain. 2012 Jul;153(7):1374-1381. doi: 10.1016/j.pain.2012.02.007. PMID: 22704600.
212. Vitaliti SM, Costantino G, Li Puma L, Re MP, Vergara B, Pinello G. Painful procedures in the NICU. J Matern Fetal Neonatal Med. 2012 Oct;25 Suppl 4:146-7. doi: 10.3109/14767058.2012.714986. PMID: 22958049.
213. Vollmer B. Management of chronic pain in newborn infants. Dev Med Child Neurol. 2020 Mar;62(3):272. doi: 10.1111/dmcn.14349. Epub 2019 Sep 5. PMID: 31489620.
214. Zeilmaker-Roest GA, van Rosmalen J, van Dijk M, Koomen E, Jansen NJG, Kneyber MCJ, Maebe S, van den Berghe G, Vlasselaers D, Bogers AJJC, Tibboel D, Wildschut ED. Intravenous morphine versus intravenous paracetamol after cardiac surgery in neonates and infants: a study protocol for a randomized controlled trial. Trials. 2018 Jun 13;19(1):318. doi: 10.1186/s13063-018-2705-5. PMID: 29895289; PMCID: PMC5998570.
215. Zhang K, Wang S, Wu L, Song Y, Cai M, Zhang M, Zheng J. Newborn infant parasympathetic evaluation (NIPE) as a predictor of hemodynamic response in children younger than 2 years under general anesthesia: an observational pilot study. BMC Anesthesiol. 2019 Jun 11;19(1):98. doi: 10.1186/s12871-019-0774-y. PMID: 31185928; PMCID: PMC6560820.

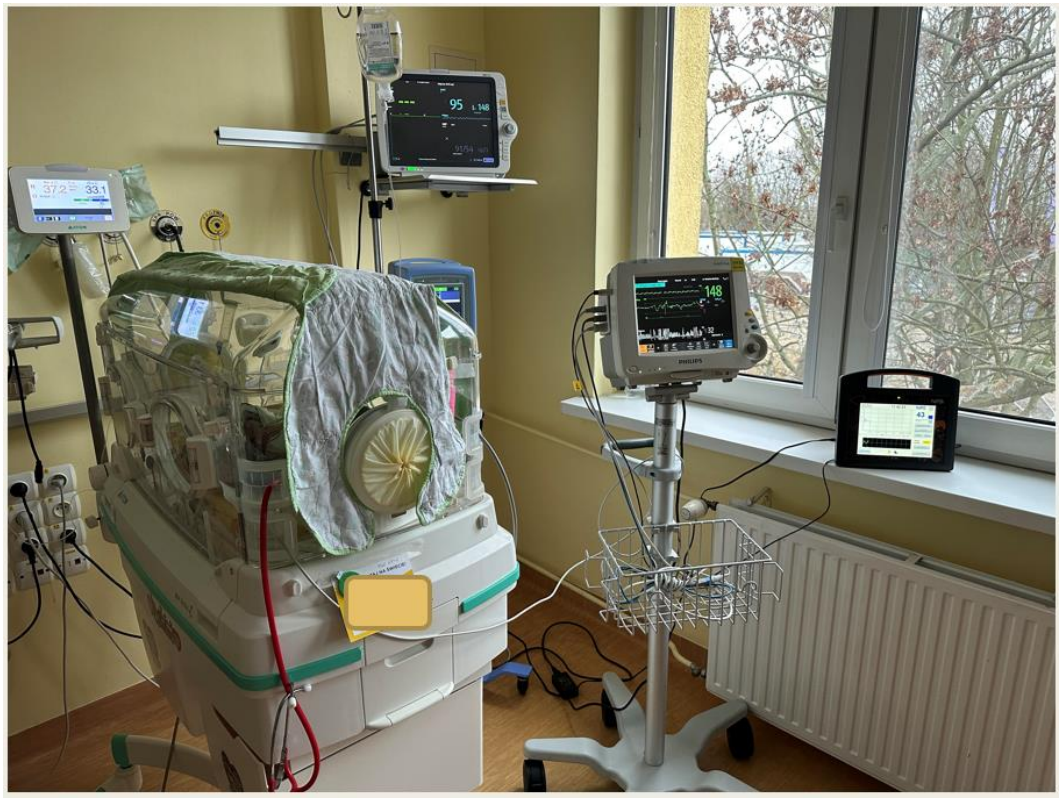
216. Zhi R, Zamzmi GZD, Goldgof D, Ashmeade T, Sun Y. Automatic Infants' Pain Assessment by Dynamic Facial Representation: Effects of Profile View, Gestational Age, Gender, and Race. J Clin Med. 2018 Jul 11;7(7):173. doi: 10.3390/jcm7070173. PMID: 29997313; PMCID: PMC6069472.

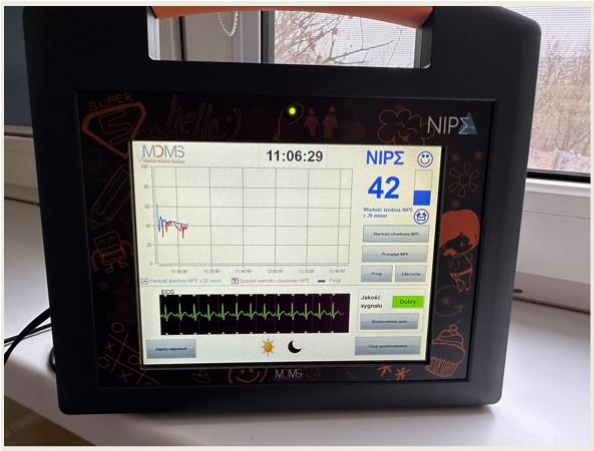
217. Ziesenitz VC, Vaughns JD, Koch G, Mikus G, van den Anker JN. Pharmacokinetics of Fentanyl and Its Derivatives in Children: A Comprehensive Review. Clin Pharmacokinet. 2018 Feb;57(2):125-149. doi: 10.1007/s40262-017-0569-6. Erratum in: Clin Pharmacokinet. 2017 Nov 24;: PMID: 28688027; PMCID: PMC5756700.

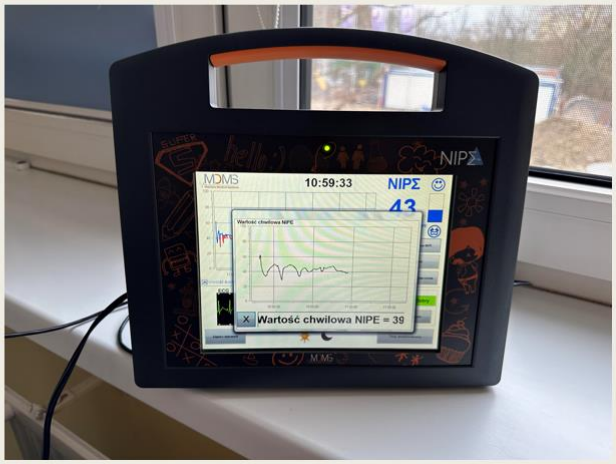
LIST OF TABLES

LIST OF FIGURES

APPENDIX 1







Above photographs were made during the patients' observation and monitoring with the NIPE pain monitor.

APPENDIX 2

Uniwersytet Mikołaja Kopernika w Toruniu
Collegium Medicum im L. Rydygiera w Bydgoszczy
KOMISJA BIOETYCZNA
Ul. M. Skłodowskiej-Curie 9, 85-094 Bydgoszcz, tel.(052) 585-35-63, fax.(052) 585-38-11

KB 265/2019 Bydgoszcz, 26.02.2019 r.

Działając na podstawie art.29 Ustawy z dnia 5 grudnia 1996 roku o zawodzie lekarza (Dz.U. z 1997 r. Nr 28 poz. 152 (wraz z późniejszymi zmianami), zarządzenia Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych (Dz.U.Nr 47 poz.480) oraz Zarządzeniem Nr 21 Rektora UMK z dnia 4 marca 2009 r. z późn. zm. w sprawie powołania oraz zasad działania Komisji Bioetycznej Uniwersytetu Mikołaja Kopernika w Toruniu przy Collegium Medicum im Ludwika Rydygiera w Bydgoszczy oraz zgodnie z zasadami zawartymi w ICH – GCP

Komisja Bioetyczna przy UMK w Toruniu, Collegium Medicum w Bydgoszczy

(skład podano w załączeniu), na posiedzeniu w dniu **26.02.2019 r.** przeanalizowała wniosek, który złożyła kierownik badania:

lek. med. Agnieszka Witulska-Alagöz,
Oddział Kliniczny Noworodków, Wcześniaków
z intensywną Terapią Noworodka wraz z Wyjazdowym Zespołem "N"
Szpital Uniwersytecki nr 2 im. dr. Jana Biziela w Bydgoszczy

z zespołem w składzie

- dr hab. n. med. Iwona Sadowska-Krawczenko, lek. med. Agnieszka Witulska-Alagöz

w sprawie badania:

„Kliniczna użyteczność i niezawodność monitom bólu NIPE u noworodków. Porównanie zastosowania indeksu NIPE, skali N-PASS. skali P1PP oraz skali EDIN w ocenie ostrego przedłużającego się bólu u przedwcześnie urodzonych noworodków."

Po zapoznaniu się ze złożonym wnioskiem i w wyniku przeprowadzonej dyskusji oraz głosowania Komisja podjęła

Uchwałę o pozytywnym zaopiniowaniu wniosku

w sprawie przeprowadzenia badań, w zakresie określonym we wniosku pod warunkiem:

- poinformowania uczestników badania o celu oraz zakresie badań i uzyskania od ich rodziców/opiekunów prawnych osobnej, pisemnej, świadomej zgody na udział w badaniu, zgodnie z obowiązującymi przepisami, datowanej najpóźniej na moment rozpoczęcia badania a nie wcześniej niż data uzyskania z Komisji Bioetycznej zgody na takie badanie;
- zachowania tajemnicy wszystkich danych, w tym danych osobowych pacjentów, umożliwiających ich identyfikację w ewentualnych publikacjach;
- sugerujemy uzyskanie podpisu uczestnika badania pod informacją o badaniu, lub sporządzenie formularza informacji i świadomej zgody na udział w badaniu na jednej kartce.

Jednocześnie informujemy, iż „Zgoda na udział w badaniu" winna zawierać m.in.: imię i nazwisko badanej osoby; Nr historii choroby pacjenta (L.ks.gł. Oddziału/Poradni) oraz datę i podpis badanej osoby (rodziców/opiekunów prawnych), a także klauzule, że uczestnik badania wyraża zgodę na przetwarzanie danych osobowych dotyczących realizacji tematu badawczego, z wyjątkiem publikacji danych osobowych.

Kierownik badania zobowiązany jest do przechowywania wszystkich dokumentów dotyczących badania przez okres dwudziestu lat.

Zgoda obowiązuje od daty posiedzenia (26.02.2019 r.) do końca 2021 r.

Wydana opinia dotyczy tylko rozpatrywanego wniosku z uwzględnieniem przedstawionego projektu; każda zmiana i modyfikacja wymaga uzyskania odrębnej opinii. Wnioskodawca zobowiązany jest do informowania o wszelkich poprawkach, które mogłyby mieć wpływ na opinię Komisji oraz poinformowania o zakończeniu badania.

Od niniejszej uchwały podmiot zamierzający przeprowadzić eksperyment medyczny, kierownik zakładu opieki zdrowotnej, w której eksperyment medyczny ma być przeprowadzony, mogą wnieść odwołanie do Odwoławczej Komisji Bioetycznej przy Ministrze Zdrowia, za pośrednictwem Komisji Bioetycznej przy Collegium Medicum im. L. Rydygiera w Bydgoszczy, w terminie 14 dni od daty otrzymania niniejszej Uchwały.

Prof. dr hab. med. Karol Śliwka

Przewodniczący Komisji Bioetycznej

Otrzymuje:
Lek. med. Agnieszka Witulska-Alagöz,
Oddział Kliniczny Noworodków, Wcześniaków
z intensywną Terapią Noworodka wraz z Wyjazdowym Zespołem "N"
Szpital Uniwersytecki nr 2 im. dr. Jana Biziela w Bydgoszczy

Lista obecności

na posiedzeniu Komisji Bioetycznej

w dniu 26.02.2019 r.

Lp.	Imię i nazwisko	Funkcja	Podpis
1.	Prof. dr hab. med. Karol Śliwka	Przewodniczący	
2.	Mgr prawa Joanna Połetek-Żygas	Z – ca przewodniczącego	
3.	Prof. dr hab. med. Mieczysława Czerwionka-Szaflarska		
4.	Prof. dr hab. med. Anna Balcar-Boroń		
5.	Prof. dr hab. med. Marek Grabiec		
6.	Prof. dr hab. med. Zbigniew Włodarczyk		
7.	Dr hab. n. med. Katarzyna Pawlak-Osińska, prof. UMK		
8.	Dr hab. n med. Maria Kłopocka		
9.	Ks. dr hab. Wojciech Szukalski, prof. UAM		
10.	Dr n. med. Radosława Staszak-Kowalska		
11.	Mgr prawa Patrycja Brzezicka		
12.	Mgr farm. Aleksandra Adamczyk		
13.	Mgr Lidia Iwińska-Tarczykowska		

Uniwersytet Mikołaja Kopernika w Toruniu

Collegium Medicum im L. Rydygiera w Bydgoszczy

KOMISJA BIOETYCZNA

Ul. M. Skłodowskiej-Curie 9, 85-094 Bydgoszcz, tel.(052) 585-35-63, fax.(052) 585-38-11

KB 694/2019 Bydgoszcz, 24.09.2019 r.

Działając na podstawie art.29 Ustawy z dnia 5 grudnia 1996 roku o zawodzie lekarza (Dz.U. z 1997 r. Nr 28 poz. 152 (wraz z późniejszymi zmianami), zarządzenia Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych (Dz.U.Nr 47 poz.480) oraz Zarządzeniem Nr 21 Rektora UMK z dnia 4 marca 2009 r. z późn. zm. w sprawie powołania oraz zasad działania Komisji Bioetycznej Uniwersytetu Mikołaja Kopernika w Toruniu przy Collegium Medicum im Ludwika Rydygiera w Bydgoszczy oraz zgodnie z zasadami zawartymi w ICH – GCP

Komisja Bioetyczna przy UMK w Toruniu, Collegium Medicum w Bydgoszczy

(skład podano w załączeniu), na posiedzeniu w dniu **24.09.2019 r.** przeanalizowała wniosek, który złożyła kierownik badania:

lek. Agnieszka Witulska-Alagöz
Oddział Kliniczny Noworodków, Wcześniaków z Intensywną Terapią Noworodka wraz z Wyjazdowym Zespołem "N"
Szpital Uniwersytecki nr 2 w Bydgoszczy

z zespołem w składzie

- dr hab. n. med. Iwona Sadowska-Krawczenko, lek. Agnieszka Witulska-Alagöz,

w sprawie badania:

„Ocena poziomu odczuwania ostrego bólu proceduralnego u noworodków w zależności od wieku płodów ego z zastosowaniem wskaźnika NIPE."

Po zapoznaniu się ze złożonym wnioskiem i w wyniku przeprowadzonej dyskusji oraz głosowania Komisja podjęła

Uchwałę o pozytywnym zaopiniowaniu wniosku

w sprawie przeprowadzenia badań, w zakresie określonym we wniosku pod warunkiem:

- poinformowania uczestników badania o celu oraz zakresie badań i uzyskania od ich rodziców/opiekunów prawnych osobnej, pisemnej, świadomej zgody na udział w badaniu, zgodnie z obowiązującymi przepisami, datowanej najpóźniej na moment rozpoczęcia badania a nie wcześniej niż data uzyskania z Komisji Bioetycznej zgody na takie badanie;
- zachowania tajemnicy wszystkich danych, w tym danych osobowych pacjentów, umożliwiających ich identyfikację w ewentualnych publikacjach;
- sugerujemy uzyskanie podpisu uczestnika badania pod informacją o badaniu, lub sporządzenie formularza informacji i świadomej zgody na udział w badaniu na jednej kartce.

Jednocześnie informujemy, iż „Zgoda na udział w badaniu" winna zawierać m.in.: imię i nazwisko badanej osoby; Nr historii choroby pacjenta (L.ks.gł. Oddziału/Poradni) oraz datę i podpis badanej osoby (rodziców/opiekunów prawnych), a także klauzule, że uczestnik badania wyraża zgodę na przetwarzanie danych osobowych dotyczących realizacji tematu badawczego, z wyjątkiem publikacji danych osobowych.

Kierownik badania zobowiązany jest do przechowywania wszystkich dokumentów dotyczących badania przez okres dwudziestu lat.

Zgoda obowiązuje od daty posiedzenia (24.09.2019 r.) do końca 2021 r.

Wydana opinia dotyczy tylko rozpatrywanego wniosku z uwzględnieniem przedstawionego projektu; każda zmiana i modyfikacja wymaga uzyskania odrębnej opinii. Wnioskodawca zobowiązany jest do informowania o wszelkich poprawkach, które mogłyby mieć wpływ na opinię Komisji oraz poinformowania o zakończeniu badania.

Od niniejszej uchwały podmiot zamierzający przeprowadzić eksperyment medyczny, kierownik zakładu opieki zdrowotnej, w której eksperyment medyczny ma być przeprowadzony, mogą wnieść odwołanie do Odwoławczej Komisji Bioetycznej przy Ministrze Zdrowia, za pośrednictwem Komisji Bioetycznej przy Collegium Medicum im. L. Rydygiera w Bydgoszczy, w terminie 14 dni od daty otrzymania niniejszej Uchwały.

Prof. dr hab. med. Karol Śliwka

Przewodniczący Komisji Bioetycznej

Otrzymuje:
lek. Agnieszka Witulska-Alagöz
Oddział Kliniczny Noworodków, Wcześniaków z Intensywną Terapią Noworodka wraz z Wyjazdowym Zespołem "N"
Szpital Uniwersytecki nr 2 w Bydgoszczy

Lista obecności

na posiedzeniu Komisji Bioetycznej

w dniu 24.09.2019 r.

Lp.	Imię i nazwisko	Funkcja/ Specjalizacja	Podpis
1.	Prof. dr hab. med. Karol Śliwka	Przewodniczący *medycyna sądowa*	
2.	Mgr prawa Joanna Połetek-Żygas	Z – ca przewodniczącego *prawniczka*	
3.	Prof. dr hab. med. Mieczysława Czerwionka-Szaflarska	*pediatra, alergologia i gastroenterologia dziecięca*	
4.	Prof. dr hab. med. Anna Balcar-Boroń	*pediatria, nefrologia*	
5.	Prof. dr hab. med. Marek Grabiec	*położnictwo, ginekologia onkologiczna*	
6.	Prof. dr hab. med. Zbigniew Włodarczyk	*chirurgia ogólna, transplantologia kliniczna*	
7.	Dr hab. n. med. Katarzyna Pawlak-Osińska, prof. UMK	*organizacja ochrony zdrowia, otolaryngologia*	
8.	Dr hab. n med. Maria Kłopocka	*choroby wewnętrzne, gastroenterologia*	
9.	Ks. dr hab. Wojciech Szukalski, prof. UAM	*duchowny*	
10.	Dr n. med. Radosława Staszak-Kowalska	*pediatria, choroby płuc*	
11.	Mgr prawa Patrycja Brzezicka	*prawniczka*	
12.	Mgr farm. Aleksandra Adamczyk	*farmaceutka*	
13.	Mgr Lidia Iwińska-Tarczykowska	*pielęgniarska*	

Uniwersytet Mikołaja Kopernika w Toruniu
Collegium Medicum im L. Rydygiera w Bydgoszczy
KOMISJA BIOETYCZNA
Ul. M. Skłodowskiej-Curie 9, 85-094 Bydgoszcz, tel.(052) 585-35-63, fax.(052) 585-38-11

KB 265/2019

Bydgoszcz, 19.04.2022 r.

Działając na podstawie art.29 ustawy z dnia 5 grudnia 1996 roku o zawodzie lekarza (Dz.U. z 1997 r. Nr 28 poz. 152 (wraz z późniejszymi zmianami), rozporządzenia Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych (Dz.U. Nr 47 poz.480) oraz Zarządzenia Nr 21 Rektora UMK z dnia 4 marca 2009 r. z późn. zm. w sprawie powołania oraz zasad działania Komisji Bioetycznej Uniwersytetu Mikołaja Kopernika w Toruniu przy Collegium Medicum im Ludwika Rydygiera w Bydgoszczy oraz zgodnie z zasadami zawartymi w ICH – GCP

Komisja Bioetyczna przy UMK w Toruniu, Collegium Medicum w Bydgoszczy

(której skład podano w załączeniu) na posiedzeniu w dniu **19.04.2022 r.** przeanalizowała prośbę o:

- przedłużenie terminu ukończenia badań do końca 2022r.

którą złożyła:

lek. Agnieszka Witulska-Alagöz
Klinika Neonatologii
Szpital Uniwersytecki nr 2 im. dr. Jana Biziela w Bydgoszczy

w sprawie badania:

„Kliniczna użyteczność i niezawodność monitom bólu NIPE u noworodków. Porównanie zastosowania indeksu NIPE, skali N-PASS. skali P1PP oraz skali EDIN w ocenie ostrego przedłużającego się bólu u przedwcześnie urodzonych noworodków".

Po zapoznaniu się ze złożonym dokumentem i w wyniku przeprowadzonej dyskusji oraz głosowania jawnego Komisja przyjęła do wiadomości podane informacje i wyraża zgodę na powyższe pod warunkami określonymi w uchwale Komisji podjętej w dniu 26.02.2019 r. oraz w ewentualnych aneksach do tejże uchwały.

Zgoda na kontynuowanie przedmiotowego badania obowiązuje do końca 2022 r.

Prof. dr hab. med. Karol Śliwka

Przewodniczący Komisji Bioetycznej

Otrzymuje:

lek. Agnieszka Witulska-Alagöz
Klinika Neonatologii
Szpital Uniwersytecki nr 2 im. dr. Jana Biziela w Bydgoszczy

Lista obecności

na posiedzeniu Komisji Bioetycznej

w dniu 19.04.2022 r.

Lp.	Imię i nazwisko	Funkcja/ Specjalizacja	Podpis
1.	Prof. dr hab. med. Karol Śliwka	*medycyna sądowa*	
2.	Mgr prawa Joanna Połetek-Żygas	*prawniczka*	
3.	Prof. dr hab. med. Mieczysława Czerwionka-Szaflarska	*pediatra, alergologia i gastroenterologia dziecięca*	
4.	Prof. dr hab. med. Marek Grabiec	*położnictwo, ginekologia onkologiczna*	
5.	Prof. dr hab. n med. Maria Kłopocka	*choroby wewnętrzne, gastroenterologia*	
6.	Prof. dr hab. med. Zbigniew Włodarczyk	*chirurgia ogólna, transplantologia kliniczna*	
7.	Dr hab. n. med. Maciej Słupski, prof. UMK	*chirurgia ogólna, transplantologia kliniczna*	
8.	Dr hab. n. med. Katarzyna Sierakowska, prof. UMK	*anestezjologia i intensywna terapia*	
9.	Ks. dr hab. Wojciech Szukalski, prof. UAM	*duchowny*	
10.	Dr n. med. Radosława Staszak-Kowalska	*pediatria, choroby płuc*	
11.	Mgr prawa Patrycja Brzezicka	*prawniczka*	
12.	Mgr farm. Aleksandra Adamczyk	*farmaceutka*	
13.	Mgr Lidia Iwińska-Tarczykowska	*pielęgniarka*	

Uniwersytet Mikołaja Kopernika w Toruniu
Collegium Medicum im L. Rydygiera w Bydgoszczy
KOMISJA BIOETYCZNA
Ul. M. Skłodowskiej-Curie 9, 85-094 Bydgoszcz, tel.(052) 585-35-63, fax.(052) 585-38-11

KB 694/2019 Bydgoszcz, 19.04.2022 r.

Działając na podstawie art.29 ustawy z dnia 5 grudnia 1996 roku o zawodzie lekarza (Dz.U. z 1997 r. Nr 28 poz. 152 (wraz z późniejszymi zmianami), rozporządzenia Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych (Dz.U. Nr 47 poz.480) oraz Zarządzenia Nr 21 Rektora UMK z dnia 4 marca 2009 r. z późn. zm. w sprawie powołania oraz zasad działania Komisji Bioetycznej Uniwersytetu Mikołaja Kopernika w Toruniu przy Collegium Medicum im Ludwika Rydygiera w Bydgoszczy oraz zgodnie z zasadami zawartymi w ICH – GCP

Komisja Bioetyczna przy UMK w Toruniu, Collegium Medicum w Bydgoszczy

(której skład podano w załączeniu) na posiedzeniu w dniu **19.04.2022 r.** przeanalizowała prośbę o:

- przedłużenie terminu ukończenia badań do końca 2022r.

którą złożyła:

lek. Agnieszka Witulska-Alagöz
Klinika Neonatologii
Szpital Uniwersytecki nr 2 im. dr. Jana Biziela w Bydgoszczy

w sprawie badania:

„Ocena poziomu odczuwania ostrego bólu proceduralnego u noworodków w zależności od wieku płodów ego z zastosowaniem wskaźnika NIPE".

Po zapoznaniu się ze złożonym dokumentem i w wyniku przeprowadzonej dyskusji oraz głosowania jawnego Komisja przyjęła do wiadomości podane informacje i wyraża zgodę na powyższe pod warunkami określonymi w uchwale Komisji podjętej w dniu 24.09.2019 r. oraz w ewentualnych aneksach do tejże uchwały.

Zgoda na kontynuowanie przedmiotowego badania obowiązuje do końca 2022 r.

Prof. dr hab. med. Karol Śliwka

Przewodniczący Komisji Bioetycznej

Otrzymuje:

lek. Agnieszka Witulska-Alagöz
Klinika Neonatologii
Szpital Uniwersytecki nr 2 im. dr. Jana Biziela w Bydgoszczy

Lista obecności

na posiedzeniu Komisji Bioetycznej

w dniu 19.04.2022 r.

Lp.	Imię i nazwisko	Funkcja/ Specjalizacja	Podpis
1.	Prof. dr hab. med. Karol Śliwka	*medycyna sądowa*	
2.	Mgr prawa Joanna Połetek-Żygas	*prawniczka*	
3.	Prof. dr hab. med. Mieczysława Czerwionka-Szaflarska	*pediatra, alergologia i gastroenterologia dziecięca*	
4.	Prof. dr hab. med. Marek Grabiec	*położnictwo, ginekologia onkologiczna*	
5.	Prof. dr hab. n med. Maria Kłopocka	*choroby wewnętrzne, gastroenterologia*	
6.	Prof. dr hab. med. Zbigniew Włodarczyk	*chirurgia ogólna, transplantologia kliniczna*	
7.	Dr hab. n. med. Maciej Słupski, prof. UMK	*chirurgia ogólna, transplantologia kliniczna*	
8.	Dr hab. n. med. Katarzyna Sierakowska, prof. UMK	*anestezjologia i intensywna terapia*	
9.	Ks. dr hab. Wojciech Szukalski, prof. UAM	*duchowny*	
10.	Dr n. med. Radosława Staszak-Kowalska	*pediatria, choroby płuc*	
11.	Mgr prawa Patrycja Brzezicka	*prawniczka*	
12.	Mgr farm. Aleksandra Adamczyk	*farmaceutka*	
13.	Mgr Lidia Iwińska-Tarczykowska	*pielęgniarka*	