Chapter

Multimodal Pain Management in Extremely Low Birth Weight Neonates after Major Abdominal Surgery

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Abstract

Limited data are available in the literature on multimodal pain management in extremely low birth weight (ELBW) neonates. This chapter aimed to summarize current knowledge about the effects of analgesics and sedatives (paracetamol, opioids, benzodiazepines and anaesthetics) on postoperative pain management (≤ 48 hours after surgery). The primary endpoints of postoperative pain management were searched using validated pain assessment instruments, such as pain intensity, excessive sedation, drug consumption or adequate rescue medication. The secondary endpoints are the safety parameters of the drugs used, while the determinants of short/long-term outcome (duration of mechanical ventilation, intraventricular haemorrhage—IVH, periventricular leukomalacia—PVL, postnatal growth restriction, stage of chronic lung disease—CLD or neurodevelopmental outcome according to the Bayley-II Scale of Infant Development at 18–24 months or developmental equivalents at early-school age) were assessed as tertiary endpoints. Additionally, one of the most important key elements of clinical science is known as clinical research study validation, including specific tools and techniques within the validation processes. This chapter focuses on postoperative multimodal pain management, including the implementation of pain assessment tools and analgesic and sedative dosing regimens needed to achieve the efficacy and safety goals of an optimal pain profile in ELBW neonates; only proven non-pharmacological procedures are not included.

Keywords: extremely low birth weight neonates, postoperative pain, COMFORTneo score, paracetamol, opioid consumption

1. Introduction

Optimal pain management is an essential requirement of the daily clinical practice of a sick neonate and one of the indicators of quality-of-life care. Records of the experience of pain and its short-term and long-term consequences for the immature organism have been increasing in the recent decades, as well as warnings of the

adverse effects of analgesics [1, 2]. A multimodal approach based on the multimodal concept of pain assessment can help to objectivate the diagnosis of pain in patients who are immature or who do not display pain due to severe illness. However, in non-verbal immature individuals, assessing pain or differentiating pain from discomfort is difficult and requires a specific approach and research into new diagnostic methods. The standard in clinical practice is evaluated scales mostly based on behavioural and physiological responses to pain. There are more than 65 assessment scales for childhood, but only a third of them are also validated for immature neonates, and significantly less for extremely low birth weight neonates (ELBW) after major abdominal surgery in particular [3]. Moreover, the choice of pain assessment tools varies among neonatal intensive care units (NICU) and countries as described, for example, in premature neonates treated for necrotizing enterocolitis (NEC) [4]. However, not all of the listed pain scales are validated, particularly for postoperative pain in ELBW.

To achieve the best possible quality in using these scoring systems at individual workplaces, implementing "evidence-based" procedures is necessary, including education with regular evaluation of the reliability and consistency of the staff in the assessment of pain since these methods are largely subjective. Objective methods such as measurement of tissue oxygenation (NIRS-near-infrared spectroscopy), skin conductance (SCM-skin conductance measurement), electroencephalography (EEG), or measurement of cortisol concentration in saliva or adrenaline, noradrenaline and cortisol determination in the blood, and physiological functions are currently auxiliary or research methods [5].

2. Clinical endpoints in neonatal postoperative pain studies

In general, clinical endpoints of pain studies are recommended to demonstrate that the introduction of validated pain together with sedation instruments while adjusting the age-appropriate dosage of analgesics and sedative drugs according to postmenstrual age (PMA) or postnatal age (PNA), and body weight leads to the

Name and type of scale, author, year, study design	**Aim of the study**	**Indicators**	**Population settings (GW, pain profile, number of patients and diagnoses)**	**Drug used/ reported**	**Commentary/ limitations on scale**
Neonatal facial coding scoring (NFCS), behavioural scale by *Peters et al., 2003 (*prospective observational study)	Validitaion of the NFCS for postoperative pain, exploration of whether the number of NFCS items could be reduced	Brow bulge, eye squeeze, open lips, mouth and tongue position and lips pursed	29 GW to 18 M, ventilated child, prolonged pain, postoperative pain, 37 patients with abdominal/ thoracic surgery	Morphine	NFCS was found as a reliable, feasible and valid tool for assessing postoperative pain. Limitation: reduction of the NFCS to 5 items increases the specificity for pain assessment without reducing the sensitivity and validity for detecting changes in pain.

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Children's & Infants' Postoperative Pain Scale (CHIPPS), behavioural scale, by *Büttner et al., 2000* (comprehensive report of 7 prospective studies)	Determination of parameters suitable indicators for postoperative pain	Crying, facial expression, trunk posture, legs movements, restlessness	35 GW to 5Y; postoperative pain, 584 children 4238 observations, diagnoses not reported	Not reported	Compared to other assessment tools (CHEOPS, OPS, CRIES, TPPPS), the CHIPPS scale items are most suitable for neonates, infants and young children in the postoperative period.
Pain Assessment Tool (PAT), multidimensional scale by *O'Sullivan et al., 2016* (non-randomised observational single-unit study)	Evaluation of the psychometric properties and clinical utility of the COVERS and PAT scales in a neonatal unit	Posture/tone, cry, sleep, face expression, colour, respiration, HR, SpO2, BP, nurse perception	23 GW to 6 M, postoperative pain, prolonged pain, 80 neonates (6 underwent surgery), diagnoses not reported	Not reported	Both COVERS* and PAT scales were reliable measures of acute pain in neonates from 24 GW. Most of the 72 assessing nurses preferred the COVERS (52%) to the PAT (16%), and 32% had no preference. Limitation: a small number of operated patients.
Modified Postoperative Comfort Score (PCS), behavioural scale, *by Guinsburg et al., 1998*, (randomised, double-blind, controlled trial)	Responses of ventilated preterm neonates to a single dose of fentanyl using physiological, humoral and behavioural measures	Sleep, facial expression, sucking, agitation, tonus, toe and finger posture, consolability	29 to 32 GW, ventilated patients, prolonged pain, 22 preterm ventilated neonates, diagnoses not reported	Fentanyl	The study demonstrated a reduction in both PCS and NFCS scores after initiation of fentanyl in preterm neonates on mechanical ventilation.
CRIES Scale, multidimensional scale, *Krechel et al., 1995*, prospective observational pilot study	Initial testing of validity and reliability of the CRIES	Crying, oxygen requires, vital signs, expression, sleeplessness	32 GW to 1 M, postoperative pain, acute pain, 24 infants following surgery (insertion of VP shunt, thoracotomy)	Not reported	The cutoff of oxygenation measure between scores 1 or 2 is set at 30%. This is not a suitable item for preterm infants with RDS/CLD. Alternatively, it can be substituted for respiratory changes in immature patients.

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Multidimensional Assessment of Pain Scale (MAPS), multidimensional scale, by *Ramelet et al., 2007,* (follow-up validation study)	Evaluation of the clinical validity and utility of the MAPS and its response to the effect of analgesics	Vital signs (HR or BP), breathing pattern, facial expressions, body movements, state of arousal	36 GW to 31 M, postoperative pain 19 postoperative critically ill children	Morphine	This study showed that MAPS like FLACC and VAS decreased similarly following rescue morphine. Limitation: internal consistency of MAPS would improve if the psychologic item was deleted.

GW—gestational week, M—month, HR—heart rate, BP—blood pressure, COVERS—crying, oxygen requirement, vital signs, expression, resting, signalling distress, RDS—respiratory distress syndrome, CLD—chronic lung disease, VP—ventriculoperitoneal shunt.

Table 1.
Studies that reported postoperative pain management in preterm neonates – the list of validated scales in postoperative pain profile.

achievement of goals in the paediatric population [6]. More recently, the Neonatal Face Coding Score (NFCS) [7], the Children's & Infants' Postoperative Pain Scale (CHIPPS) [8], the Pain Assessment Tool (PAT) [9], the Modified Postoperative Comfort Score (PCS) = Clinical Scoring System [10], the CRIES scale [11] and the Multidimensional Assessment of Pain Scale (MAPS) [12] were validated for the treatment of postoperative pain in preterm neonates, of which only the PAT scale for extremely low birth weight neonates (ELBW, less than 1000 g, less than 28 weeks of gestation), respectively (**Table 1**). Therefore, in the ELBW cohort, it is also recommended that pain management, including assessment, re-evaluation, prevention, and treatment of a given pain profile (postoperative pain lasting 0–48 hours after surgery) adopted from other preterm neonates, seems to be best described by clinical goals. Primary endpoints are efficacy parameters (excessive, optimal or failed management) as measured by a validated postoperative score (PAT) or some validation processes are needed to be implemented using the COMFORTneo scale or the Numerical Rating Scale (NRS) for a given pain profile, and the effect of paracetamol on opioid consumption during the first 48 hours after surgery also. Secondary endpoints are, for example, safety parameters of the analgesic drugs (e.g., paracetamol hepatotoxicity or bradycardia <80/min, and hypotension defined as mean blood pressure < 10th percentile for opioids). Tertiary endpoints are parameters of long-term morbidity (e.g., intraventricular haemorrhage—IVH, periventricular leukomalacia—PVL, the severity of chronic lung disease, postnatal restriction of growth, prolonged pulmonary ventilatory support, abdominal discomfort, enteral nutrition and breastfeeding, length of hospital stay, and mental and psychomotor development in 12–24 months or death), and more recently, the correlation between total cumulative opioid dose from birth to the period of developmental equivalent assessment of cognitive, language, motor and executive functions at early-school age or later (**Figure 1**) [13].

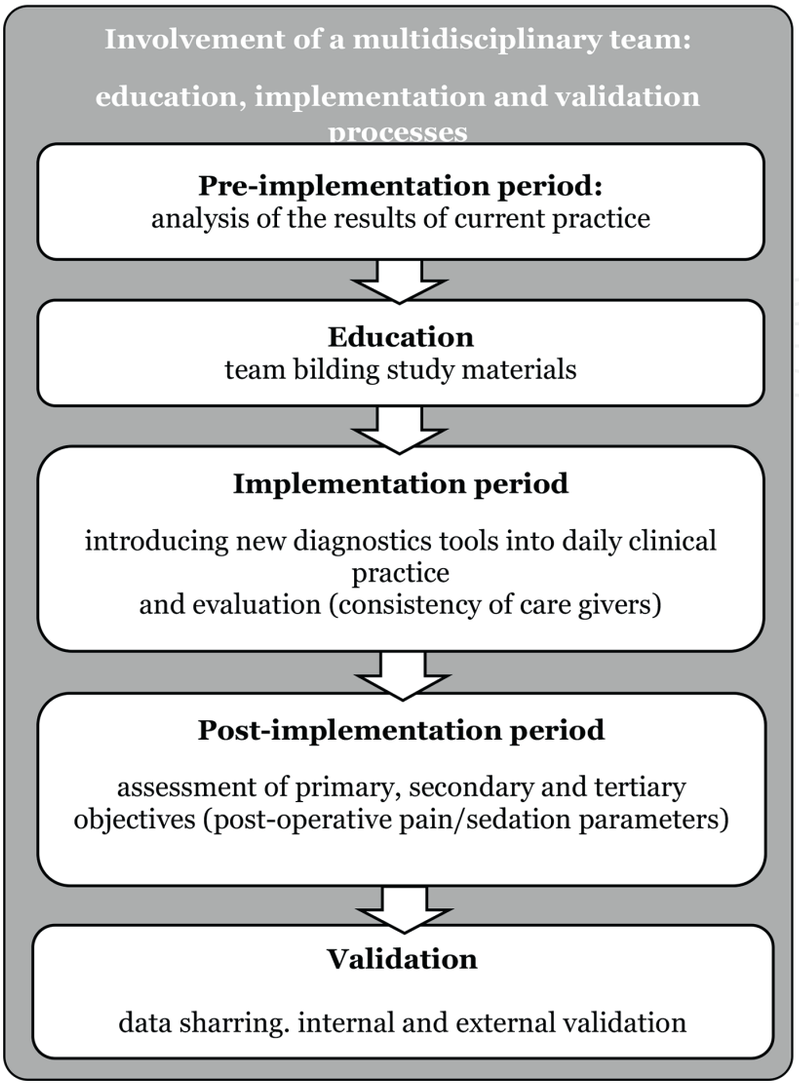

Figure 1.
Multimodal pain management in extremely low birth weight infants after major abdominal surgery and team involvement. Primary objectives are postoperative pain/sedation efficacy parameters (pain lasting 0–48 hours after surgery). Secondary objectives are safety parameters of the analgesics and sedative drugs used (pain lasting 0–48 hours after surgery). Tertiary objectives are parameters of long-term (monitoring parameters evaluated for 12–24 months) and early-school age (5 years of age).

3. Pain scales validated in ELBW population

3.1 Pain assessment tool (PAT)

The PAT scale is a scoring system developed and evaluated by Hodgkinson in 1994, originally in a group of 20 term neonates following surgery. The study found that PAT effectively quantified neonates' pain and reflected nurses' perceptions of it [14]. The scale incorporates both behavioural and physiological items and includes a score based on the caregiver's judgement to capture individual reactions and evaluations of the nurse who cared for the patient over time. The tool has ten parameters (see **Table 1**) that are scored on a scale of 0 to 2, with minimum and maximum scores of 0 and 20. Scores greater than 5 indicate some non-pharmacological methods to provide adequate comfort, and scores greater than 10 require adjustment of the analgesia. Later, Spence and O'Sullivan demonstrated that the PAT is a reliable

and valid tool in various groups of NICU patients (both surgical and nonsurgical, preterm and term). The PAT is a clinician-friendly Pain Assessment Tool for all groups of critically ill infants in the NICU; moreover, according to the literature, it is the only scale validated for the postoperative pain profile in extremely low birth weight neonates [9, 15]. However, we find certain limitations in the small sample size of the studied surgical ELBW patients and in the possible impact of the variability of physiological thresholds across gestational/postmenstrual ages (e.g. chronic lung disease and oxygenation requirements).

3.2 COMFORTneo

In 2004, a modified COMFORT-behavioural scale (COMFORTneo) was created and validated in a population of preterm infants to provide the following definition: behavioural distress encompasses all behaviours of negative affect associated with pain, anxiety and fear. And distress may occur in the absence of pain [16]. The COMFORTneo scale consists of 6 behavioural items: alertness; calmness/agitation; muscle tone assessment by observation of movements of extremities, crying/respiratory response in ventilated patients, body movements and facial expressions. Total scores range from 6 to 30 (1 to 5 for each item) and the cutoff score reflecting pain/distress is ≥14. A score ≤ 9 reflects possible oversedation. Testing of internal consistency of the scale was good and concurrent validity with the NRS (Numeric rating scale) was adequate in terms of persistent or prolonged pain and sedation in neonates from the 23rd to 43rd weeks of gestational age. COMFORTneo scale and physiological measurements could be clinically useful pain instruments for the neonatal intensive care unit (NICU) environment and critically ill neonates in the postoperative period.

3.3 Numerical rating scale (NRS)

The NRS quantifies pain on a scale from 0 to 10 based on an individual patient's pain experience; the assessment of pain intensity is as follows: no pain = 0, mild pain = 1–3, moderate pain = 4–6, and severe pain ≥7. Various pictorial adaptations of the NRS mimicking facial expressions are used in young children. For non-verbal individuals, the quantification of pain rests in the hands of caregivers or parents according to the typical patient's pain behaviour. The tool's accuracy depends on the parents and nurse's ability to observe and describe the patient's response to pain in an individual way [17]. As some validation studies show, this simple tool is a good instrument to specify the nature of discomfort (pain or stress) as an additional tool along with validated behavioural and multidimensional scales in the population of preterm neonates [3]. The NRS is a useful instrument in the multimodal assessment of pain in premature neonates; moreover, the possibility of parental involvement in pain management improves current practice in NICUs.

4. Adjuvant objective methods in neonatal pain studies

4.1 Near-infrared spectroscopy (NIRS)

Cortical activity specifically associated with the affective component of nociception, i.e. with the negative emotional experience of pain (e.g. the area of the cingula, insula, prefrontal cortex), does not always have to be correlated with the

discriminative-executive component, which we can assess from the behaviour of the neonates [18, 19]. NIRS is a non-invasive method of optical measurement of local changes in tissue oxygenation in real time. Roué described the most significant correlation between pain and changes in NIRS parameters in 113 full-term healthy neonates during venipuncture. The other measurements performed in this study (skin conductance, heart rate, cortisol in saliva) rather represented a prolonged stress reaction to pain [20]. Bartocci demonstrated primary and secondary somatosensory cortex activation after venipuncture in premature neonates (28-36th gestational weeks), with an intensity inversely proportional to gestational age [21]. Other CNS centres participating in the discriminative and affective components of nociception were also studied using this method. Yuan demonstrated a correlation between pain and NIRS changes in the prefrontal cortex during circumcision in healthy mature neonates [22]. NIRS is a non-invasive objective method that could most closely correlate with the cortical response to a painful stimulus.

4.2 Physiological functions

Heart and respiratory rate, SpO2 and blood pressure are measured continuously as a part of standard postoperative monitoring of vital functions. Physiological responses to pain stimuli and their correlations were described in multivariate analyses. In full-term infants, physiological measurements were not necessarily well-correlated with behavioural responses. A positive correlation was found between SpO2 and NIRS parameters (HbO2) [20]. Different findings were described in neonates between 28 and 36 weeks of gestation. Preterm infants were more likely to exhibit desaturation or apnoea in response to a painful or stressful stimulus [21]. Therefore, these different pain response profiles should be considered in future research.

4.3 Skin conductance measurement (SCM)

Changes in electrical skin conductance measured on the palmar side of the hands and soles appear suitable for objective pain evaluation [23, 24]. The activation of the sympathetic nervous system by painful stimuli leads to the activation of eccrine sweat glands and an increase in electrical skin conductivity. These changes could be detected in infants <28 + 0 of gestational age and seem to be able to differentiate between pain and discomfort [25]. Surprisingly, it seems that conductance parameters do not correlate with gestational age, and their changes have been described in neonates as early as 22 gestational weeks. The major limitation of the method is the inability to determine basal skin conductance in this population [26].

5. Pharmacological treatment in neonatal postoperative pain studies

Pharmacological treatment of pain together with sedation in the postoperative period is governed by international recommendations for the treatment of moderate to severe pain (postoperative pain profile lasting for 48 hours) for mechanically ventilated neonates, and a combination of systemic analgesics (opioids and non-opioids) and sedatives or regional anaesthesia (levobupivacaine) for some surgeries are selected [27]. Pharmacological treatment includes slow IV boluses, intermittent dosing or using continuous infusion with the commonly used opioid—morphine, and synthetic opioids—fentanyl, or sufentanil in some intensive care units, the effects of

which are expressed as morphine potency. Therefore, morphine-equivalent doses are also calculated to achieve an analgesic effect, but the dosage will vary according to the postnatal age (PNA) of the neonate; for example, in neonates younger than 10 days, it is recommended to reduce the initial dose of morphine or sufentanil [28, 29]. More recently, alpha agonists (dexmedetomidine and clonidine) can also be considered, as well as intravenous paracetamol, recommended to be given to all patients regularly and in a dose corresponding to the postmenstrual age (PMA) with an initial loading dose and a maintenance dose (see paracetamol) [30, 31]. Adjusting the dosage of analgesics and sedative drugs is guided by the scale of pain and sedation and doses should be titrated to appropriate effects. In case of PAT score > 10 or COMFORTneo and NRS scores indicating discomfort (≥ 14 or more ≥4), the rate of opioid infusion is increased in individual steps by a certain percentage (%) up to the maximum age-appropriate dose to achieve the desired effect. As a rescue ("rescue") analgesic treatment in case of severe pain (i.e. PAT >10, COMFORTneo ≥ 22, NRS ≥ 7), a bolus of opioids or a second-choice drugs (e.g. ketamine, dexmedetomidine, clonidine or propofol) are used intravenously so that the target values of PAT (≤10), COMFORTneo (9–13) points and NRS (0–3 points) are achieved. On the contrary, for COMFORTneo scores corresponding to excessive sedation (<9) and NRS ≤3, the opioid infusion rate should be reduced, for example by a certain percentage (%) based on assessment. The analgesic/sedation concept in ELBW after abdominal surgery has its pharmacological aspects that strongly correlate with changes in drug disposition, which are the consequences of, for example, extreme immaturity, period of peri−/postoperative stress (metabolic, hormonal, etc.) related to abdominal causes of surgery (e.g. NEC, spontaneous intestinal perforation—SIP) or inflammation (changes in CYP 450 activity) or physiological changes in ventilation, circulation, renal and hepatic functions and as expected increased permeability of the blood-brain barrier to analgesics and sedatives in ELBW neonates. In this vulnerable population, therefore, measuring the effectiveness and safety of the drugs used is extremely important. In the following section, drugs are selected with a focus on drug characteristics, clinical indication, reported efficacy and safety and drug dosage in premature and ELBW neonates, respectively, after abdominal surgery. Complex therapy includes non-pharmacological interventions, sucrose, the most used intravenous analgosedative drugs (except ibuprofen), and significantly less used epidural analgesics; therefore, the knowledge about analgosedative use still missing in this population will be summarized.

5.1 Morphine

A natural opiate alkaloid with a rapid and prolonged peak onset of action (20 minutes after IV single injection) acting, for example 3–5 hours after IV single injection used in neonates for postoperative pain, for specific conditions such as necrotizing enterocolitis (NEC) and neonatal abstinence syndrome (NAS) [32, 33]. Pharmacodynamics is highly dependent on the dosage form and route of administration (epidural, intravenous, subcutaneous, intramuscular, oral or rectal) with a broad peak of onset of action after administration lasting between 20 and 90 min and a duration of 3–20 hours. However, ELBW neonates lack reports on efficacy and safety (e.g. evidence of benefits for poor neurologic outcomes) [34, 35]. Respiratory depression and hypotension have been described with continuous infusion. Therefore, lower doses are generally recommended in premature neonates. Dosing: analgesia [36, 37], 0.05–0.1 mg/kg/dose every 4–6-8 hours for intermittent dosing while for continuous IV infusion initial dose 0.01 mg/kg/dose is titrated to the maximum

0.03 mg/kg/hour (some authors suggested 0.015–0. 020 mg/kg/hour). Initial IV infusion rates of 0.010 mg/kg/hour are acceptable for neonates younger than 1 week. Neonates older than 1 week tolerate 0.015 mg/kg/hour, whereas older infants may tolerate 0.020–0.040 mg/kg/hour. Supplemental IV boluses of as much as 0.050 mg/kg may be administered for episodes of breakthrough pain in mechanically ventilated neonates who are receiving morphine by means of continuous infusion. For example, Kinderformularium recommends morphine dosing for preterm neonates < 37 weeks GA as an initial dose of 0.050–0.100 mg/kg followed by continuous infusion of 0.003–0.020 mg/kg/hour continuous infusion.

5.2 Fentanyl

Fentanyl is a synthetic effective opioid with high potency to morphine, a rapid-acting onset (peak onset 3–4 min after IV single injection) with medium-long duration (30 min after IV single injection) used for acute procedural, postoperative, and prolonged pain profile, and specific conditions (ECMO) in neonates. Adverse effects include apnoea, increased chest rigidity and respiratory depression that more often described when fentanyl is administered as an IV bolus of 0.001–0.002 mg/kg than when it is given as a continuous IV infusion of 0.001–0.002 mg/kg/hour while fentanyl causes less likely systemic hypotension than morphine. The first report of a cohort of very preterm neonates (23–30 gestational age) evaluated the association between cumulative neonatal exposure to fentanyl by neurodevelopmental and socioemotional outcomes in children at 5 years of age. However, according to the authors, the conclusions of this study were still ambiguous [38]. Dosing: analgesia [39], intermittent slow IV push 0.0005–0.003 mg/kg/dose, continuous infusion 0.0005–0.002 mg/kg/hour; sedation, slow IV push 0.001–0.004 mg/kg/dose may be repeated every 2–4 hours, continuous analgesia/sedation initial 0.001–0.002 mg/kg then 0.0005–0.001 mg/kg/hour. The mean required dose is 0.00064 mg/kg/hour <34 GA. During ECMO IV push 0.005–0.010 mg/kg and 0.001–0.005 (max 0.020) mg/kg/hour were reported due to known drug tolerance in this population. Additionally, the Kinderformularium database recommends fentanyl dosing for preterm neonates < 37 weeks GA: an initial dose of 0.0005–0.003 mg/kg followed by continuous infusion 0.005–0.003 mg/kg/hour continuous infusion.

5.3 Sufentanil

A synthetic, short-acting opioid agonist with a rapid onset of action (peak onset 5–6 min after IV single injection) and with a medium-long duration (30 min after IV single injection) more potent than fentanyl or morphine used for general and intraoperative anaesthesia, and analgesia/sedation in mechanically ventilated neonates and neonatal ECMO. Adverse effects are somewhat similar to those reported with fentanyl (bradycardia, hypotension, hypertension, cardiac arrhythmia, CNS depression, respiratory depression, chest wall rigidity, seizures and burst-suppression EEG pattern). Sufentanyl doses are not validated for premature neonates. Dosing: analgesia/sedation, in mechanically ventilated premature neonates 26–34 weeks IV loading dose 0.0005 mg/kg over 10 minutes followed by 0.002 mg/kg/hour continuous infusion [40], or in ventilated full-term neonates, sufentanil LD of 0.002 mg/kg and MD of 0.00029 mg/kg/hour was reported, but dosage regimen was recommended to be verified in clinical trials for analgesia in full-term neonates [41]. A 0.0005 mg/kg IV bolus and a continuous infusion of 0.0002 mg/kg/hour for 24 hours have been

recommended for postoperative anaesthesia (Anand 1992). The Kinderformularium database recommends the dosage of sufentanil for young infants and children (from 1 month to 18 years)—an initial dose of 0.0002—0.0005 mg/kg (maximum 0.001 mg/kg) and a loading dose (LD) in ventilated patients: 0. 0003–0.002 mg/kg/dose slowly IV over 30 seconds. If necessary, additional doses of 0.0001–0.001 mg/kg/dose can be given up to a maximum (cumulative) dose of 0.005 mg/kg in major procedures [42].

5.4 Paracetamol

Paracetamol (acetaminophen) is a non-opioid drug commonly used drug to treat mild to moderate pain management (peak onset for analgesia from 5 to 10 min to 1 hour after IV single injection) and fever (peak onset antipyretic effect within 30 min after IV single infection) and pain profile with duration (4–6 hours for analgesia). It is successfully used for postoperative pain or as "rescue" treatment post-operatively, as reported in ELBW, and additionally, for narcotic and morphine-sparing effect, respectively [43]. At the same time, the administration of paracetamol only for procedural indications in neonates is under discussion [44]. Paracetamol is recommended for ELBW neonates intravenously post-operatively on a regular schedule as a slow bolus injection over 15 minutes, although evidence of paracetamol dosing for pain relief is also known for oral and rectal administration in younger neonates than 32 weeks of postmenstrual age (PMA). Concerns about adverse effects are justified (circulatory, hepatic, renal, respiratory, etc.), and dosing must be adjusted to the appropriate age of the neonate even though the production of hepatotoxic metabolites is lower due to reduced CYP450 activity [45]. Dosing: the loading dose of paracetamol for premature neonates is 20 mg/kg, and the maintenance dose (MD) is based on PMA: in neonates less than 32 weeks (PMA), the maintenance dose will be 7.5 mg/kg every 8 hours, in neonates ≥32 weeks of PMA 10 mg/kg every 8 hours [31]. Similarly, the Kinderformularium database recommends paracetamol dosing for premature neonates PMA < 32 weeks as a starting dose: 12 mg/kg/dose, once, and MD as 24 mg/kg/day in 4 doses intravenously [42].

5.5 Midazolam

Midazolam is, among other sedative drugs, still commonly used benzodiazepine with rapid onset action (within 1–5 min after IV single injection, maximum 5–7 min) and short duration (20-30 min after IV single injection) and widely used for sedative (acute/prolonged), anxiolytic and anticonvulsive effects and amnesia before induction of anaesthesia and procedural sedation used as intermittent dosing or continuous IV infusion. Adverse effects include cardiovascular (hypotension), seizure like-activity, myoclonic jerks in preterm neonates, nystagmus, agitation or bronchospasm. Dosing: sedation IV 0.05–0.15 mg/kg may be repeated every 2–4 hours, continuous IV infusion 0.01 to 0.06 mg /kg/hour, and the dose should be titrated to achieve the desired effect [46]. The Kinderformularium database recommends midazolam dosing for preterm neonates < 32 weeks GA: initial dose up to 8 weeks postnatal age (PNA) is 0.05 mg/kg/dose over 30 minutes to avoid the risk of hypotension if given more rapidly, and MD: 0.03 – 0.1 mg/kg/hour, continuous infusion [42].

5.6 Dexmedetomidine

An alfa (α-2) adrenergic agonist with rapid onset action (its onset of action is less than 5 minutes, and the peak effect occurs within 15 minutes) used for sedation,

reversible hypnotic effect and added on analgesia profile for procedural sedation and is increasingly used post-operatively in neonates. The various reported side effects are hypotension, hypertension, nausea, vomiting, bradycardia, atrial fibrillation, and pyrexia, but no respiratory depression effects and less anaesthetics and fentanyl consumption were reported in some patient cohorts after abdominal surgery treated with dexmedetomidine perioperatively [47]. Dosing: initial bolus IV 0.00005–0.001 mg/kg over 10 min and continuous infusion 0.0002–0.0008 mg/kg/hour (max. 0.0012 mg/kg/hour). For example, the Kinderformularium database recommends dexmedetomidine dosing for preterm neonates < 37 weeks GA: LD 0.0002–0.0003 mg/kg/dose over 10 min and MD: 0.0002–0.0003 mg./kg/hour, continuous infusion dose based on effect and side effects. Max: 0.001 mg/kg/hour [42]. Use of LD (starting dose) depends on any concomitant use of other sedatives and the current and desired level of sedation.

5.7 Clonidine

An alfa (α-2)-adrenergic agonist with a rapid onset action and short duration (the peak action occurs in 10 minutes and lasts for 3–7 hours after IV single dose) that is used for its anxiolytic and sedative effects and safety profile (preventing respiratory depression or haemodynamic instability), treatment for NAS, although, withdrawal symptoms were reported similar but less likely to benzodiazepines and opioids [48]. There are various and unknown mechanisms related to its sedative and add-on analgesic effects. Dosing: 0.001–0.003 mg/kg over 10 min (max. 0.0012 mg/kg/day for intermittent dosing) or LD of 0.001 mg/kg over 10 min and 0.0005–0.001 mg/kg/hour [49, 50] in a term neonate. Also, the Kinderformularium database recommends clonidine dosing for term neonates only: LD 0.0005 mg/kg/hr., continuous infusion and MD up to a maximum of 0.003 mg/kg/hour, continuous infusion. If a rapid effect is desired, a loading dose of 0.001 mg/kg can be given in 15 minutes. Clonidine is reported to have a risk of rebound phenomenon after its discontinuation, so prevention of this phenomenon is recommended by slow weaning.

5.8 Ketamine

A general anaesthetic drug with a direct action on the cortex and limbic system with a rapid onset of action (within 30 seconds after IV injection), peak onset of action (5–6 min), and a medium-long duration following the IV single dose (5–10 minutes for anaesthesia) or over 15–30 min for analgesia after IM administration. Adverse effects are described among others (arrhythmias, bradycardia, tachycardia, hyper/hypotension, increased salivation, vomiting, tonic-clonic movements, airway obstructions, respiratory depression and hallucinations, etc., difficult to objectify in ELBW neonates) [51]. Dosing: LD 0.5–1.0 mg/kg (maximum 2 mg/kg) while using more smaller doses followed by IV continuous infusion 0.25 mg/kg/hour is more recently recommended [27] for a term neonate. The Kinderformularium doses are LD at induction of anaesthesia: 0.5–1 mg/kg/dose once and MD 0.5–3 mg/kg/hour continuous infusion [42]. Alternative: intermittent administration: 0.25–0.5 mg/kg/dose every 10–15 minutes [52].

5.9 Chloral hydrate

A hypnotic and sedative with CNS depressant properties similar to barbiturates. The onset of action is 10–20 minutes, peak effect within 30–60 min, and duration

4–8 hours. Adverse effects are described as CNS symptoms (paradoxical excitement), EEG is not influenced, withdrawal syndrome is known for its prolonged use, and warnings are reported in the paediatric population [53–55]. It is used orally and rectally in neonates and is common for procedural sedation. The risk of accumulation is known after 3 days in preterm and 7 days in term neonates, and hypoxia may occur within 24 hours of administration in some reports. Dosing: 25–75 mg/kg max. á 12 h is administered orally/rectally in full-term neonates only 30 mg/kg/dose, once, and if necessary, repeat after 30 minutes with 15–30 mg/kg/dose [56, 57].

5.10 Propofol

Propofol (2,6-diisopropylphenol) is an anaesthetic drug with a fast onset of action (within 30 seconds) after IV injection and short-term anaesthetic effect (3–10 min) depending on the dose, infusion rate and duration of administration in mechanically ventilated neonates. Propofol is primarily used for induction/maintenance anaesthesia, acute/procedural sedation (e.g. endotracheal intubation), secondary to the treatment of seizures. However, side effects were described, including cardiovascular (dose-dependent profound and prolonged hypotension) in preterm neonates (25.8–31.7 gestational weeks) treated with or without hemodynamic instability and/or NEC if propofol was used as a premedication for sedation at intubation, then metabolic (hypertriglyceridemia), respiratory (apnoea) and life-threatening episodes were reported (propofol syndrome, CNS symptoms, etc.). [58, 59]. Dosing: for IV induction and the maintenance IV infusion with a starting dose of 1.0 and 1.5 mg/kg to a maximum of 3.5 mg/kg /hour. [60].

6. Conclusion

In recent decades, many findings have been published on pain management in the neonatal population, increasingly in preterm neonates, but data are almost lacking for ELBW neonates and the relevant pain profile (postoperative pain) in this population. Except for clonidine, ketamine and chloral hydrate, drug doses have been published for some drugs (morphine, dexmedetomidine and fentanyl), especially in neonates below 37 weeks GA, and for paracetamol and midazolam in preterm neonates less than 32 weeks of PMA and GA respectively while insufficient data are available for fentanyl derivatives (sufentanil) in preterm neonates and especially in ELBW neonates. This period of life has specific pharmacological challenges due to extreme immaturity and unpredictable drug efficacy and safety, so any contribution of knowledge and established drug databases to optimize pain management in extremely low birth weight neonates using a multimodal approach to pain management is essential.

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Conflict of interest

The authors declare no conflict of interest.

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