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Abstract	Inadequate pain management in neonatal life impairs neurodevelopmental outcome because it alters pain thresholds, pain- or stress-related behavior, and physiological responses later in life. However, there are also emerging animal experimental and human epidemiological data on the impact of analgo-sedatives on neuro-apoptosis and impaired neurodevelopmental outcome. As a consequence, the management of neonatal pain is in search of a new balance, and these conflicting observations are the main drivers to tailor our pain management in neonates. Adequate pain management is based on prevention, assessment, and treatment with subsequent reassessment. Issues related to prevention and assessment tools are covered. Non-pharmacological (e.g., complementary interventions like facilitated tucking, nonnutritive sucking) and pharmacological (e.g., acetaminophen, opioids, ketamine, propofol) treatment modalities were reviewed and reflect the increased knowledge on neonatal pain management. Each topic ends with some *take-home messages* that in part also reflect our personal opinion on the current status of this topic.

Keywords (separated by " - ")	Neonatal intensive care unit (NICU) - Neonate - Pain - Pain assessment tools - Premature infant pain profile (PIPP) - Douleur Aiguë du Nouveau-né (DAN/EDIN) score - COMFORT score - The Modified Behavioral Pain Scale (MBPS) - Visual Analogue Scale (VAS) - Numeric Rating Scales (NRS) - Heart rate - Oxygen saturation - Facial expression - Limb movement - Vocalization - Nonnutritive sucking - Swaddling - Containment - Multisensorial stimulation - Analgesia - Sedation - Analgo-sedation - Bispectral index (BIS) - Near-infrared spectroscopy (NIRS) - American Academy of Pediatrics (AAP) - Neonatal Facial Coding Score (NFCS) - Ketamine - Eutectic Mixture of Local Anesthetics (EMLA) - Postnatal age - Postmenstrual age - Propofol - Pharmacokinetics - Pharmacodynamics - Remifentanil - Chloral hydrate - Morphine fentanyl - Benzodiazepines - Midazolam - Dexmedetomidine - Acetaminophen (paracetamol) - Infant-centered care (ICC) index - Infant pain management (IPM) index - Intubation-surfactant-extubation (INSURE) - Continuous positive airway pressure (CPAP)

Sedation in the Neonatal Intensive Care Unit: International Practice

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Karel Allegaert and John van den Anker

Introduction

Why Do Neonates Need Procedural Analgo-sedation?

About 30 years ago, the myth that immaturity of the nervous system precluded neonates from pain perception and its negative effects was rejected by Anand et al. when he documented that inadequate analgesia during and following surgery (patent ductus arteriosus clipping as model) resulted in increased mortality and morbidity [1]. It subsequently became apparent that the negative effects of inadequate analgesia were not limited to neonatal life, but were also observed in later infancy. Inadequate management of pain in (pre)term neonates alters and affects thresholds of pain, pain- or stress-related behavior, and physiological responses and contributes to impaired neurodevelopmental outcome [1–5].

The ontogeny of the nervous system is based on a complex pattern of cell proliferation, migration, differentiation, and selective cell death, including apoptosis. Functional development relates to a balance of excitatory and inhibitory signals. Due to maturational plasticity of the nociceptive systems throughout infancy, nociceptive input may cause population-specific lasting alterations in pain processing [1–5]. Alterations in biological covariates (e.g., peripheral and central somatosensory function and modulation, brain structure and connectivity) and psychosocial covariates (e.g., gender, coping style, mood, parental response) that affect pain perception and expression were identified in former preterm neonates [5]. Consequently, effective analgesia is relevant not only because of ethical reflections or human empathy, but it is also a crucial and integral part of medical and nursing care to neonates.

However, there is also emerging evidence on the relation between the exposure to narcotics and impaired neurodevelopmental outcome, resulting in a CATCH-22 scenario [6]. Experimental data from animals provide evidence that chronic morphine exposure in perinatal life results in reduced brain volume, decreased neuronal packing density, and less dendritic growth and branching. This is associated with learning and motor disabilities. In contrast, opioid receptor blockade through naloxone results in increased brain size and more pronounced dendritic arborization. Similar animal experimental data have been reported for other analgo-sedatives, including benzodiazepines, ketamine, inhalational anesthetics, propofol, barbiturates, or combinations of such analgo-sedatives. Alterations are in part drug and dose dependent, and there is an age-related window of vulnerability for apoptosis or dendritic changes [7–10].

The extrapolation of these observations in animals to the human (pre)term newborn is obviously hampered by several limitations. An *association* between major neonatal surgery (number of interventions, disease severity) and neurodevelopmental impairment has been observed. However, exposure to analgo-sedatives is only one of the factors associated with this negative outcome [11, 12]. In the (pre)term newborn, it seems that the limbic system hereby has a specific vulnerability for overexposure to pain, stress, or drugs (narcotics, analgesics, or sedatives). This vulnerability is likely because

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the maturational changes in the limbic structures evolve at a very fast rate throughout the last trimester of pregnancy until late infancy. The limbic system, hippocampus, and the regions connected to the hippocampus are essential as switch board to encode, consolidate, and retrieve memory. Intriguingly, these types of memory deficits are frequently observed in former preterm neonates [6].

Others have extended these long-term impact research concept to include medical procedure-related pain and nociception in later life in preterm neonates [2, 13]. Using functional magnetic resonance imaging during a tonic heat stimulus, the cerebral pain responses in three sets (neonatal intensive care unit (NICU) preterm, NICU full term, no NICU admission) of each nine children were compared [13]. Former preterm infants had significantly higher activations than controls in primary somatosensory cortex, anterior cingulate cortex, and insula. This exaggerated brain response was pain-specific since this was not observed during non-painful warmth stimulation [13]. Similarly, and using a term matched-control design in 43 former extreme preterm neonates, Walker et al. documented that there were differences in somatosensory perception in childhood [14]. Interestingly, these differences were in part local (e.g., thermal and mechanical hyposensitivity around a thoracotomy scar) and in part more general (thermal hyposensitivity). As another relevant and reassuring piece of information, a brief exposure to general anesthesia compared to awake-regional anesthesia (GAS study) for inguinal hernia repair in infants (<60 weeks postmenstrual age) was not associated with any difference in neurodevelopmental outcome (IQ assessment) at the age of 5 years [15].

The currently available observations strongly suggest that early pain contributes to neurodevelopmental outcome, pain thresholds, pain- or stress-related behavior, or physiological responses in later life and that insufficient pain management should be avoided. Effective pain management therefore remains an important indicator of the quality of care provided to neonates, not only from an ethical but also from an outcome perspective [14, 15].

Although there is an obvious difference between sedation and analgesia, the available assessment tools and practices cannot always fully discriminate between sedation and analgesia. The increased awareness that neonates feel pain, the ethical obligation to treat this pain with analgesics, the growing body of evidence demonstrating that untreated neonatal pain can lead to altered reactivity to pain that persists throughout infancy and childhood, as well as the need for a humane management of neonates resulted in the development of guidelines to promote the use of analgesics in neonates [3, 16]. The main objectives of sedation and analgesia are reduction of pain, stress, and irritability and promotion of physiologic stability. In the long-term, reduced stress, as well as improved physiologic stability, is believed to minimize the risks of neurological injury and death. Alleviation of pain is a fundamental human right, regardless of age [17–19].

Despite the ethical issues, the increasing awareness regarding pain management in neonates, and the availability of published guidelines for the treatment of procedural pain, preterm neonates still experience pain resulting in short- and long-term detrimental effects. The discrepancy between the available knowledge (relevance of adequate analgo-sedation, validation of techniques) and the bedside practices has been illustrated by Carbajal et al. [20]. This research group reported epidemiological data on the incidence of painful and stressful procedures and its management in the first 14 days of admission that were prospectively collected within a 6-week period (2005–2006) in 430 neonates admitted to tertiary care NICUs in the Paris region of France. This epidemiological study resulted in a median of 115 procedures for each neonate during the study period and 16 procedures per day. Of these, each neonate experienced a median of 75 painful procedures during the study period and 10 painful procedures per day of hospitalization. Of the 42,413 painful procedures, 2.1% were performed with pharmacological-only therapy, 18.2% with non-pharmacological only therapy, 20.8% with pharmacological and non-pharmacological therapy, and 79.2% without specific analgesia. 34.2% were performed while the neonate was receiving concurrent analgesic or anesthetic infusions for other reasons [20]. Prematurity, category of procedure, parental presence, surgery, daytime, and day of procedure after the first day of admission were associated with greater use of specific pre-procedural analgesia, whereas mechanical ventilation, noninvasive ventilation, and administration of nonspecific concurrent analgesia were associated with lower use of specific procedural analgesia [20]. Consequently, the authors concluded that large numbers of painful and stressful procedures were performed, of which the majority were not accompanied by analgesia. The conclusions and epidemiological findings are very similar to the data published by Simons et al. collected 5 years earlier. Based on a dataset in 151 preterm neonates, each neonate was subjected to 14 (SD 4) procedures per day [21]. Despite the fact that most of these procedures were estimated to be painful, preemptive analgesia was provided to fewer than 35% of neonates per study day, while about 40% of the neonates did not receive any analgesic therapy during their NICU stay [21].

Similar results were reported when practices were compared between two time intervals in a same region. Survey data for the years 2004 and 2010 on analgesia policy and practices for common invasive procedures at Italian NICUs were compared to ascertain the extent to which neonatal

analgesia for invasive procedures has changed since the publication of Italian guidelines [17, 22]. Based on paired data on 75 NICUs, the practice of pain monitoring became more common. However, only 21% and 17% of NICUs routinely assessed pain during mechanical ventilation and after surgery, respectively. Similarly, the routine use of medication for major invasive procedures was still limited (35% of lumbar punctures, 40% of tracheal intubations, 46% during mechanical ventilation), and postoperative pain treatment was also inadequate. Consequently, the authors concluded that despite the improvements in neonatal analgesia practices in Italy since national guidelines were published, pain is still largely undertreated and underscored [17, 22]. Within the EUROPAIN (cohort 2012–13) consortium, this extensive variability in practices has been confirmed [23].

Take-Home Messages: Why a Focused Chapter on Neonatal Analgo-sedation?

Neonates do feel pain. It has even been described that neonates are even more vulnerable to pain. These more vulnerable neonates are precisely those that are most exposed to painful interventions. The subjectivity inherent to pain assessment in neonates probably further contributed to the wide variety of practices. The specific characteristics of neonates warrant a focused approach, because:

- The lack of verbalization is likely one of the most important obstacles for the proper diagnosis and treatment of pain and distress in newborns. Pain in the newborn is usually not easily recognized and remains commonly under- or untreated [18, 19]. In general, if a procedure is painful in adults, it should be considered painful in neonates.
- Proper analgo-sedation in newborns is associated with a reduction in morbidity and mortality [1]. Compared with older children and adults, neonates, especially preterm neonates, likely have a higher sensitivity to pain. This is due to a maturational delay in suppressive descending corticospinal tracts compared to ascending sensory spinocortical tracts. Moreover, the impact of inadequate managed pain during neurodevelopment results in a higher susceptibility to long-term effects of nociceptive stimulation [4].
- By virtue of their nature, newborns completely depend on its caregivers (parents, health-care professionals) to recognize their needs. This includes aspects related to comfort, stress reduction, and absence of pain and should cover evaluation/assessment, prevention, and managing of pain and distress [14].
- The appropriate use of environmental, behavioral, and pharmacological interventions can prevent, reduce, or eliminate pain and may improve comfort. This means that such interventions need to be validated, compared, and integrated in routine nursing and clinical care. Promotion of clinical research, knowledge diffusion, and validation of the effectiveness of implementation strategies to improve analgo-sedation remains crucial [7, 14].
- Simultaneously with this emerging evidence on the appropriate use of analgo-sedatives, neonatal care itself also is an evolving discipline. There is a shift towards less invasive care, reflected by introduction of minimal enteral feeding to shorten duration of parenteral nutrition, while duration of endotracheal ventilation was shortened through early nasal continuous positive airway pressure (CPAP) or the INSURE (*in*tubation-*sur*factant-*e*xtubation) or LISA (less invasive surfactant administration) approach. In term neonates, whole body hypothermia became a valid technique to improve outcome following perinatal asphyxia. These shifts in clinical care induced a shift in pharmacokinetic covariates and pharmacodynamic endpoints [16].
- Analgesic dosing regimens should take into account the severity and type of pain, the therapeutic window of the analgesic, but also the age or developmental state of the (pre)term newborn. Translation of these concepts to safe and effective pharmacological analgesia in neonates necessitates thorough understanding of the principles of clinical pharmacology. Growth, weight, or size and maturation or age evolve and profoundly affect pharmacokinetics (concentration-time profile, absorption, distribution, metabolism, and excretion) and pharmacodynamics (concentration-effect profile, objective assessment).
- Besides age and size, comorbidity, co-administration of drugs, or genetic variations in drug-metabolizing enzymes, transporters, and receptors further contribute to the extensive interindividual variability in pharmacokinetics or dynamics [20]. When we apply the concept of developmental pharmacology to analgo-sedatives in neonates, this means that this should be a balanced decision based on systematic assessment of effects and side effects (PD), followed by titrated administration of the most appropriate analgesic(s)(PK) with subsequent reassessment (PD) to adapt and further titrate exposure and effects [7, 14, 24].
- Inadequate management of pain in early human life contributes to impaired neurodevelopmental outcome and alters pain thresholds, pain- or stress-related behavior, and physiological responses. However, there are also emerging animal experimental data on the impact of exposure to analgo-sedatives on the incidence and extent of neuro-apoptosis [3, 11, 12]. Since this association has

also been suggested in humans, the pharmacological treatment of neonatal pain is in search of a new equipoise since these "conflicting" observations are the main drivers to further reconsider our current treatment regimens.

Effective management of pain remains an important indicator of the quality of care provided to neonates. Effective treatment includes appropriate assessment (section "Assessment of Distress and Pain in Neonates"), prevention when possible (section "Preventive Strategies"), and managing of pain and distress based on both non-pharmacological (section "Complementary Interventions") and pharmacological (section "Pharmacological Interventions") techniques with subsequent tailoring to the needs and characteristics of the individual newborn (Fig. 18.1). We will first discuss issues related to assessment, followed by illustrations on the potential relevance of preventive strategies. The main body of this chapter summarizes the available data on non-pharmacological (complementary) and pharmacological interventions in neonates. In the final part, there is a discussion about a research agenda on analgo-sedation in neonates, and this part finishes with a procedure-specific review (immunization procedure, sedation for imaging, circumcision, routine blood sampling in the maternity ward) in the case studies. For each section, the available scientific information is provided, while the subsequent "key messages" in part also reflect our subjective opinion.

Assessment of Distress and Pain in Neonates

Limitations of Assessment of Distress and Pain in Neonates

Although this is still an area of active research, there is at present no easy, widely accepted, uniform approach or assessment tool to screen and quantify pain or distress in neonates [25]. The gold standard of pain assessment, i.e., verbal self-report, cannot be used in preverbal patients: neonates can only express their distress or pain, while it is up to the caregiver to subsequently read and recognize these signs [3, 26]. To structure such assessment and to make this more objective, pain assessment tools have been constructed. However, assessing pain or distress in neonates remains one of the most challenging issues that caregivers, clinical researchers, and parents have to address. In the absence of a universally accepted, valid, reliable, and bedside useful single biologic measure, we need to rely on pain assessment tools. Such assessment techniques are based on behavioral observations and/or physiologic and hormonal measurements. In general, multidimensional assessment tools (i.e., both behavioral and physiologic items) are used. Pain assessment tools that quantify pain-related behavior include but are not limited to muscle tone, facial expression, position of the eyebrows and mouth, crying, muscular activity, or consolability. In Table 18.1,

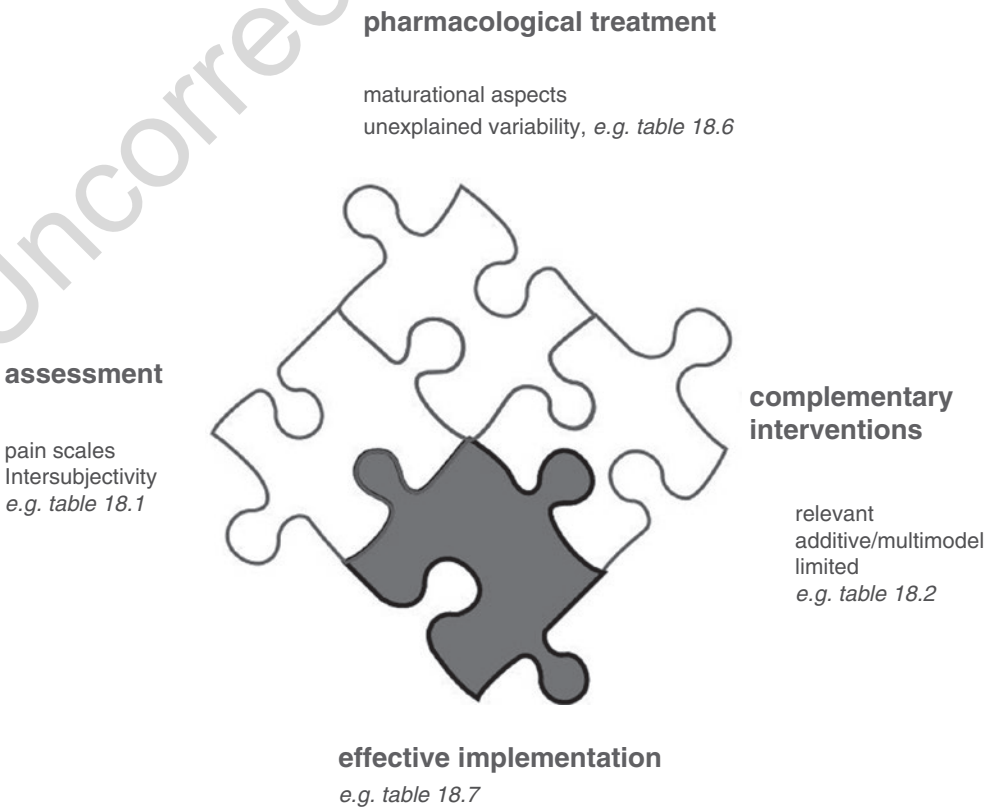

Fig. 18.1 Assessment, complementary interventions, pharmacological treatment, and effective implementation fit together like puzzle pieces to result in effective management of pain or distress in neonates

Table 18.1 Characteristics of some frequently reported multidimensional pain assessment tools in (pre)term neonates and young infants and indicators assessed [27–39]

Score	Indicators assessed
PIPP-R [27, 28]	Premature infant pain profile, procedural pain score. Gestational age, behavioral state, heart rate, saturation, brow bulge, eye squeeze, nasolabial furrow
AN [29]	Douleur Aiguë du Nouveau-né. Procedural pain score. Facial expression, limb movement, vocalizations, and attempts to vocalization
MBPS [30]	Modified Behavioral Pain Scale. Procedural pain score. Facial expression, cry, and body movements
COMFORT [31]	Prolonged pain, including postoperative pain. Alertness, calmness/agitation, respiratory response, crying (only in non-ventilated cases, physical movement, muscle tone, facial tension (initially behavioral and physiologic measures)
COMFORT-neo [32]	Prolonged pain, adapted from the COMFORT score. Similar to the comfort score, 7 behavioral items are scored, but muscular tone is scored based on observations (clenched toes/fists), while "no movement" was converted to "no or minor movement" to adapt for specific characteristics of neonates. One of the behavioral items is either crying (in non-ventilated cases), or respiratory response (in ventilated cases)
CRIES [33]	Crying, requires increased oxygen, increased vital signs, expression, sleeplessness. Prolonged pain, including postoperative pain
FLACC [34]	Face, legs, activity, cry, consolability. Prolonged pain, including postoperative pain
N-PASS [35]	Neonatal pain, agitation, sedation scale. Procedural and prolonged pain, including ventilated or postoperative. Indicators assessed are crying/irritability, behavior state, facial expression, extremities (tone) and vital signs (heart rate, respiratory rate, blood pressure, oxygen saturation)
NIPS [36]	Neonatal Infant Pain Scale. Facial expression, cry, breathing patterns, arm movements, leg movements, and state of arousal
EDIN [37]	Echelle de la Douleur inconfort Nouveau-Né. Facial activity, body movements, quality of sleep, quality of contact with nurses, consolability
NFCS [38]	Neonatal Facial Coding Scale. Brow bulge, eye squeeze, nasolabial furrow, open lips, stretch mouth (vertical and horizontal), lip purse, taut tongue, chin quiver
BPSN [39]	Bernese Pain Scale for Neonates. Respiratory pattern, heart rate, oxygen saturation, alertness, duration of cry, time to calm, skin color, brow bulge with eye squeeze, posture

we provide a list of commonly used multidimensional pain scales in neonates [27–39].

Major limitations of pain scale are the impact of maturation and disease status on these indicators. In general, severe illness or immaturity will result in a less robust expression. In addition, these indicators have a limited specificity and even sensitivity for pain [40]. Distress or agitation (e.g., hunger, cold, wet diaper) will also result in similar behavioral responses, while Slater et al. nicely illustrated that there is a difference between nociception and pain expression ("facial non-responders") in neonates who underwent heel lancing. Pain assessment tools focus on aspects of pain expression, not necessary equal to or reflecting nociception [40, 41]. Finally, most of these assessment tools have been validated in a context of acute procedural pain and may be less effective to unveil acute persistent or chronic pain in neonates. Since most research focuses primarily on acute pain, in clinical practice, there remains the challenge of assessing prolonged and/or persisting pain [26].

The relatively immaturity in preterm neonates results in the fact that facial behavior following either noxious or non-noxious inputs looks in its appearance very similar to care providers [42]. Preterm neonates do not display pain behaviors and physiologic indicators as reliably and specifically as full-term infants [43].

Research can potentially provide more sophisticated measurement tools, e.g., bispectral index (BIS) monitor, near-infrared spectroscopy (NIRS), electroencephalography (EEG), or skin conductance to quantify sedation or pain in neonates [42]. BIS is a multifactorial tool derived from electroencephalographic findings and quantifies sedation, but has not been validated in infants in the first year of life. NIRS provides information on regional cerebral blood flow and oxygen extraction [44, 45]. However, this is only a surrogate marker for either sedation or pain. Skin conductance can be influenced by sweat glands and may hereby reflect autonomic activation, but in neonates also relates to differences in humidity of the incubator and maturational changes. Until such equipment becomes available following validation, we need to rely on clinical assessment tools [46, 47].

Despite the limitations discussed, there has been an extremely fast growth in the number of clinical assessment tools to quantify pain in neonates [26, 43]. This proliferative growth likely reflects the dilemma related to the current absence of a universally accepted, valid, reliable, and bedside useful single biologic measure. Of the >40 pain scores that are available, a few should be selected for different populations and contexts [43].

In the neonatal clinical setting, we suggest that the premature infant pain profile (PIPP) [27, 28], the Douleur Aiguë du Nouveau-né (DAN), Echelle de la Douleur inconfort Nouveau-Né (EDIN) score [29, 37], and the COMFORT score [31, 32] are the most commonly used pain assessment tools. The Modified Behavioral Pain Scale (MBPS) has also been frequently used to assess pain expression in young infants [30]. Table 18.1 provides an overview of the variables included in these and a few additional pain scores [27–39].

Despite the name, the PIPP score has been developed to measure procedural pain in both preterm and term neonates, but does consider gestational age (≥36, 32–35, 28–31, or <28 weeks, respectively) as one of the indicators to quantify

the pain expression, hereby reflecting the fact that pain expression is less robust in more immature preterm infants. The PIPP score is based on seven indicators (three behavioral (all facial actions: brow bulge, eye squeeze, nasolabial furrow), two contextual (age, behavioral state), and two physiologic (heart rate, oxygen saturation)), with each a four-point scale, resulting in a range of 0–28. The behavioral state is classified based on 15 seconds of observations, while (changes in) heart rate, oxygen saturation, brow bulge, eye squeeze, and nasolabial furrow are observed in a 30 seconds time interval [27, 28]. For this score, good construct validity is combined with excellent inter- and intra-rater reliability [48]. The DAN and EDIN scores are multidimensional *behavioral* pain assessment tool initially developed to assess procedural pain in (pre) term neonates without a priori differentiation between both subpopulations [29, 37]. It hereby combines issues related to facial expression (0–4 points), limb movements (0–3 points), and vocal expression (0–3 points) characteristics, resulting in a maximum total DAN score of 10. The scoring on vocal expression does contain specific instructions for intubated newborns.

The reliability and validity of the COMFORT scale as a postoperative pain instrument has been assessed in 158 neonates and toddlers following major abdominal or thoracic surgery [31]. Trained nurses rated the children's pain at 3, 6, and 9 h after surgery in the pediatric surgical intensive care unit using the COMFORT and a Visual Analogue Scale (VAS) for pain. Interrater reliability of the COMFORT items proved to be good for all items with the exception of the item "Respiratory response," which was moderate (Kappa 0.54). Further analysis showed that the structure of the COMFORT data was best represented by three latent variables: COMFORT "behavior" with loadings from the behavioral items (alertness, calmness, respiratory response/crying, physical movement, muscle tone, and facial tension) and separate latent variables for "heart rate baseline" (HR) and "mean arterial blood pressure baseline" (MAP). Factor loadings of the items were invariant across time, indicating stability of the structure. The latent variables COMFORT "behavior" and VAS pain were highly interrelated indicating congruent validity. Stability of COMFORT "behavior" and VAS pain was moderate [31]. Because prolonged pain in neonates remains a challenge, a modified version of the COMFORT-behavior scale (COMFORT-neo) for its psychometric qualities in the NICU setting has subsequently been assessed [32]. This scale is reliable to assess prolonged acute pain and discomfort in newborns [49]. In a clinical observational study, nurses assessed patients with COMFORT-neo and Numeric Rating Scales (NRS) for pain and distress, respectively. Based on almost 3600 triple ratings in 286 neonates, interrater reliability turned out to be good. Concurrent validity was demonstrated by adequate and good correlations, respectively, with NRS-pain and NRS-distress (r = 0.52, 95% CI 0.44–0.59, and r = 0.70, 95% CI 0.64–0.75, respectively). COMFORT-neo cutoff scores of 14 or higher (score range is 6–30) had good sensitivity and specificity (0.81 and 0.90, respectively) using NRS-pain or NRS-distress scores of 4 or higher as criterion [36]. The MBPS quantifies facial expression, limb movements, and vocalizations or attempt at vocalizations and has mainly been developed and applied for procedural pain expression in young infants (2–6 months) (e.g., immunizations) [30].

Implementation of Assessment

Among others, the American Academy of Pediatrics states that ongoing assessment of pain is essential for adequate pain treatment. Despite this, there remains a gap between the available knowledge and the effective implementation of pain assessment in neonates, as reflected in several epidemiological studies [50]. To further illustrate the relevance of such studies, we refer to three published observational studies from Italy, Australia, and the Netherlands [17, 22, 51, 52]. A report from Italian NICUs suggest that systematic assessment of pain is routinely applied in only 20% neonates on mechanical ventilation, in 12% of neonates on nasal CPAP, and only 14% of neonates in a postoperative setting [17, 22]. Similar observations were reported from Australia, based on data available from 196 hospitals. A clinical practice guideline informed the management of neonatal pain in 76 (39%) of the hospitals. There was wide variation in their use between the states and a significantly higher use of such a guideline in higher-level care units. A pain assessment tool was used in only 21 (11%) of the units with greater use in the higher level care neonatal intensive care units (50%) and surgical neonatal intensive care units (80%). Awareness of breastfeeding for procedural pain was reported by 90% of the 196 respondents, while 78% reported that it was actually used. Awareness of sucrose for procedural pain was lower than breastfeeding at 79%, with 53% reporting that they used sucrose in their unit. Overall, 89% of the respondents reported that breastfeeding or sucrose was used for the management of procedural pain in their units [51]. Finally, Ceelie et al. assessed compliance to a pain management protocol in a cohort of 200 postoperative infants in the Rotterdam unit [52]. A mean of 11 assessments in the first 72 h postoperatively per patient had been recorded. A total of 2103 pain assessments were retrieved, of which 1675 (79.7%) suggested comfort. Compliance to the protocol (reassessment and correct medication) was provided in 66 (15.4%) of the 428 assessments suggesting pain or distress. Consequently,

the authors concluded that the postoperative pain protocol applied in their ICU appeared to be effective, while full compliance to the protocol remained only marginal, possibly leading to undertreatment of pain [52].

More recently, the EUROPAIN study (2012–13 cohort) reported on different aspects of pain management in the NICU setting and hereby documented that assessment of continuous pain occurred in less than 1/3 units and in less than 10% of admitted newborns [53]. The subsequent interventions showed wide variation in sedation, and analgesia practices between units and countries, with opioid, benzodiazepine, and muscular relaxant exposure to 74%, 25%, and 25% in intubated newborns, respectively, associated (but at least in part reflecting disease severity) with prolonged ventilation in exposed cases were compared to nonexposed cases [23].

Take-Home Messages on Pain Assessment

- Assessment of pain and reassessment after an intervention is an essential part of effective pain treatment in neonates [26, 43].
- Multidimensional pain scales like the PIPP, DAN, and COMFORT (neo) are the most commonly used pain assessment tools, but a variety of scores is mentioned in Table 18.1 [27–39].
- Currently available assessment tools are suboptimal, since they are based on pain expression, not necessary reflecting nociception [40, 43].
- *Not the assessment, but the implementation of assessment is the bottleneck*: strategies to optimize the implementation of systematic objective assessment of pain are urgently needed [50].

Preventive Strategies

Several complimentary interventions as well as adaptations of procedural techniques may be used to prevent pain and stress in newborns. In this way, such interventions may reduce the need for pharmacological interventions or improve their effectiveness (synergism). Such strategies include light and noise reduction, nesting or swaddling, rationalizing and minimizing patient handling (e.g., preserving free periods for sleep, avoid consecutive blood sampling, clustered care), consider the use of central venous catheters instead of multiple peripheral perfusions, individualized monitoring techniques (vital signs registration, blood pressure measurement interval), tailoring nursing techniques (e.g., frequency endotracheal suctioning, skin and wound care, tape and wound dressing), and promoting skin-to-skin contact between the newborn and its parents. The growing body of evidence on specific non-pharmacological (complimentary) interventions is discussed elsewhere (section "Complementary Interventions"). We here would like to stress the relevance to consider methodological, procedural aspects as a potential powerful tool to reduce the need for analgo-sedation. This is illustrated by endotracheal suctioning and venous blood sampling. Other examples are the use of a lens instead of an eye lid distractor to reduce the pain response during ROP screening [54]. An assisted delivery with Kiwi OmniCup versus metal ventouse is associated with a decreased neonatal pain response [55].

Endotracheal suctioning is a pain- and stressful procedure, commonly associated with pronounced fluctuations in vital signs in ventilated newborns. Cordero et al. compared two endotracheal suctioning frequencies in preterm neonates and concluded that there was no benefit of systematic, routine suctioning compared to suctioning as needed [56]. Based on these findings, an evidence-based protocol whereby ventilated newborns were suctioned only as needed based on clinical indicators was developed. This protocol was subsequently introduced as part of the collaborative quality improvement initiative [57] and resulted in a significant decrease in the number of procedures performed. Four-handed care to facilitate containment during endotracheal suctioning was also associated with a decrease in stress and defense behavior and an increase in self-regulatory behavior [58]. Besides frequency of endotracheal suctioning or complimentary interventions, technical issues like disconnection or deep versus shallow endotracheal suctioning have been evaluated in two Cochrane meta-analyses [59, 60]. Based on observations in 252 infants and using a crossover design in which suctioning with or without disconnection was compared, it was concluded that suctioning without disconnection resulted in a reduction in episodes of hypoxia (RR 0.48), and fewer infants experienced episodes where the transcutaneous partial pressure of oxygen ($TcPO_2$) decreased by >10% (RR 0.39). Endotracheal suctioning without disconnection resulted in a more limited change in heart rate (weighted mean difference 6.77) and a reduction in the number of infants experiencing a decrease in heart rate by >10% (RR 0.61). The number of infants having episodes of bradycardia was also reduced during closed suctioning (typical RR 0.38). There is evidence to suggest suctioning without disconnection from the ventilator improves the short-term outcomes when focusing on vital signs, likely reflecting reduced stress response [59]. In contrast, there is no evidence on the benefits or risks of deep versus shallow suctioning of endotracheal tubes in ventilated neonates [60].

Venous blood sampling is an even more commonly performed procedure in neonates. Besides complementary interventions like non-nutritive sucking, sucrose, or containment, the technique used for blood sampling is also of relevance

as illustrated in 2 studies in 120 and 100 healthy term neonates, respectively. In the study of Larsson et al., venipuncture was compared to a small or large lancet, respectively, in neonates who underwent testing for phenylketonuria. Successful sampling with only one skin puncture was successful in 86%, 19%, and 40% of the cases, while median time to finalize collection was 191, 419, and 279 seconds, respectively. This also resulted in lower pain scores in the venipuncture group (Neonatal Facial Coding Score, NFCS) (247) compared to both heel lancing techniques (333 and 460, respectively) [61]. Similar observations were reported by Ogawa et al. [62]. A population of 100 healthy term neonates were randomly allocated one of 4 groups (venipuncture versus heel lancing, oral sucrose versus water). Using this design, the NFCS was significantly lower in the venipuncture group (230 versus 580). The lancing group with sucrose even still had higher scores compared to the venipuncture without sucrose (470 versus 230). Finally, when heel lancing is applied, an automatic lancet is more effective (lower pain, enhanced cerebral oxygenation) compared to a manual technique [63].

Take-Home Messages

- *Methods matter*: besides pharmacological and complimentary interventions, adaptations of techniques or procedures applied can be a powerful tool to reduce pain and/or discomfort. This has been documented based on randomized controlled trials for both endotracheal suctioning and venous blood sampling, but have also been reported for other types of procedures [59–62].

Complementary Interventions

Increased awareness of a persistent high number of painful procedures routinely performed in neonates during their stay in the unit, combined with concerns regarding potential adverse effects of pharmacological agents, and the desire to actively involve parents in the care of their newborns resulted in a surge and evaluation of alternative, non-pharmacological interventions for acute, procedural pain in neonates [64, 65]. This fits into a biopsychosocial model of acute pain management in infants (DIAPR-R = The Development of Infant Acute Pain Responding-Revised) model, as recently summarized by Bucsea and Riddell [66].

Non-pharmacological interventions, such as environmental or behavioral, may have a wide applicability for neonatal pain management, but should mainly be considered as "bundle" care approaches. These interventions are not necessarily substitutes or alternatives for pharmacological interventions but are complimentary. Non-pharmacological interventions can reduce neonatal pain indirectly by reducing the total amount of noxious stimuli to which infants are exposed and directly, by blocking nociceptive transduction or transmission or activation of descending inhibitory pathways, or by activating attention and arousal systems that modulate pain. In neonates, non-nutritive sucking, including sucrose, glucose, or human milk, swaddling and containment procedures, sensory stimulation, and the kangaroo method can be considered as complementary interventions.

Non-nutritive Sucking, Sucrose, Glucose, and Human Milk

There is limited evidence to support the use of non-nutritive sucking in preterm and high-risk full-term infants as an intervention to promote behavioral outcomes and gastrointestinal function or feeding tolerance, but it has been linked to a reduced length of hospital stay and improved pain management. Non-nutritive sucking in preterm and high-risk full-term infants does not appear to have any short-term negative effects, but data on long-term outcome in high-risk full-term and preterm infants are not available. Based on the available results, it is very reasonable to utilize pacifiers and non-nutritive sucking for pain management in high-risk full-term and preterm infants [67, 68].

The most extensively evaluated and likely – at present – most relevant non-pharmacological intervention for procedural pain relief in neonates is the oral administration of sucrose (12–24%), glucose (30%), or mother's milk, either or not combined with non-nutritive sucking (pacifier), but we should have realistic expectations on the magnitude of the effect. In a recent systematic review on the effectiveness and safety of non-pharmacological methods of pain relief in newborn infants (search terms: "infant," "premature," "pain," "acupuncture," "skin-to-skin contact," "sucrose," "massage," "musical therapy," and "breastfeeding"), 24 studies were included [69]. Most resulted in some degree of analgesia, but many were ineffective, and some were even detrimental. Sucrose, for example, was often ineffective but was more effective than music therapy, massage, breast milk (for extremely premature infants), or noninvasive electrical stimulation acupuncture. There were also conflicting results for acupuncture, skin-to-skin care, and musical therapy. Most non-pharmacological methods of analgesia provide add-on benefit to result in pain relief, but none are completely effective, and there is no clearly superior method [69].

It is believed that the effects of sucrose and non-nutritive sucking are mediated by both endogenous opioid and

non-opioid systems. There is meta-analytical evidence in support of the use of oral administration of sucrose 24%, glucose 30%, or mother's milk in combination with a pacifier shortly before a painful procedure (e.g., blood sampling, nasogastric tube placement, immunization/vaccination) as an effective tool for procedural analgesia in neonates [70–75]. The observations on the use of sucrose during heel lancing hereby are much more common compared to other interventions or procedures.

Consequently, it became the most frequently applied intervention for procedural analgesia in neonates and, to a more limited extent, in infants. To make this more effective, this should be combined with the use of a pacifier, and the sweet solution should be administered on the tongue shortly before the initiation of the procedure. The paradigm to wait for 2 minutes after initiation of sucrose administration has more recently been questioned [76].

When compared with local analgesia/Eutectic Mixture of Local Anesthetics (EMLA) or systemic acetaminophen (paracetamol) or morphine, glucose/sucrose and non-nutritive sucking results in the most prominent decrease in pain scores during heel lancing [70–75]. More moderate positive results were obtained during immunization in infancy (2–6 months), resulting in the guidelines to use sweet solution with a pacifier (or other facility to maintain suctioning) only up to the age of 4, max 6 months [77].

All these studies used neonatal pain scores to quantify pain expression, assuming that this also reflects differences in nociception. In the preverbal setting, the gold standard of pain assessment, i.e., verbal rapport of the individual patient, cannot be applied. The neonate is unable to say and can only show ("express") his/her distress or pain. Consequently, it is up to the caregiver to recognize ("read") these signs or to look for the absence of signs of comfort. To read these signs in a structured way, several sedation or pain scales have been developed and validated. In general, all currently clinical available tools focus on aspects of pain behavior or expression (e.g., motor activity, facial expression, motor tone, vital signs), not necessary reflecting pain perception or nociception [26, 40, 43]. This methodology-related conflict between different methods to assess pain (nociception versus pain expression) in neonates has been illustrated in the paper of Slater et al. on sucrose during heel lancing in neonates [41].

In a randomized controlled setting (sucrose versus water), the authors confirmed the significant decrease in PIPP scores when sucrose was applied. However, when more sophisticated assessment tools (spinal nociceptive reflex withdrawal activity *or* cortical evoked response, i.e., specific brain activity evoked by one time-locked heel lance with electroencephalography as identified by principal component analysis) were applied, no differences between both groups could be unveiled. We are aware that this study has been criticized on its sample size (insufficiently powered) and methods (EEG evaluated limited to 0.5 seconds before up to 1 seconds after the heel lance), but at least, it re-illustrates that pain expression (as assessed by pain scores) is not equal to nociception [41]. At least, the behavioral effect of sucrose can likely be explained by a pain modulation effect and hereby provides evidence for the presence of pain-modulating systems in neonates. In essence, caregivers responsible for neonates and infants should be aware of the fact that early pain experience is one of the covariates of interindividual variability in neurodevelopmental outcome, e.g., pain thresholds, pain- or stress-related behavior, and physiological responses in later life, while Slater et al. illustrated that sucrose or glucose are indeed not perfect as analgesics and that they are likely in part effective through distraction and in part through endogenous opioid release [41].

Swaddling and Containment Procedures

Van Sleuwen et al. performed a meta-analysis on the available knowledge on the impact of swaddling in excessive crying infants [78]. These authors concluded that swaddled infants arouse less and sleep longer. Preterm infants have shown improved neuromuscular development, less physiologic distress, better motor organization, and more self-regulatory ability when they are swaddled [79]. When compared with massage, excessively crying infants cried less if swaddled, and swaddling can soothe pain in infants. It is supportive in cases of neonatal abstinence syndrome and infants with neonatal cerebral lesions. It can be helpful in regulating temperature but can also cause hyperthermia when misapplied. Another possible adverse effect is an increased risk of the development of hip dysplasia, which is related to swaddling with the legs in extension and adduction. In the neonatal intensive care setting, data are somewhat more contradictory. In a meta-analysis, it seems that swaddling has a pain relieving effect, but it was maintained longer in term compared to preterm neonates [78, 79].

In Table 18.2, we provide an illustrative overview of studies to illustrate the effectiveness and limitations of facilitated tucking in (pre)term neonates, either or not combined with or compared to other complementary interventions, like oral sucrose, or non-nutritive sucking [80–93]. Methodologically, the majority of these studies were not blinded and applied a crossover type of design, while order effects in these crossover type of studies are only rarely reported. However, the available evidence points to a modest reduction in pain

Table 18.2 Overview of studies to illustrate the effects and limitations of facilitated tucking in (pre)term neonates, either as single intervention or when combined with complementary interventions (oral sucrose, non-nutritive sucking) [80–93]

Reference	Study design
Liaw et al. (2012) [80]	Randomized, controlled crossover trial in 34 preterm (29–37 weeks) neonates to compare non-nutritive sucking to facilitated tucking with routine care on pain response (premature infant pain profile, PIPP, score) after heel lancing. Both facilitated tucking and non-nutritive sucking resulted in a reduced pain response, but non-nutritive sucking was more effective as single intervention
Liaw et al. (2012) [81]	Randomized, controlled trial to assess the impact of non-nutritive sucking, sucrose, and facilitated tucking either alone or combined on infant's sleep-wake states before, during, and after heel-stick procedures in 110 infants (26.4–37 weeks gestational age). The combination of non-nutritive sucking, sucrose, and facilitated tucking resulted in the best preservation of the infant's sleep-wake states
Sundaram et al. (2013) [82]	Randomized controlled crossover pilot study in 20 preterm (28–36 weeks) neonates to compare the impact of facilitated tucking to no intervention on the PIPP score 30, 60, 90, and 120 seconds after the heel stick. Facilitated tucking resulted in significantly lower PIPP scores throughout time (8.8, 7.5, 7.2, 6.6, and 11.2, 10.7, 10.6, and 10.5).
Hill et al. (2005) [83]	Randomized, crossover study in 12 preterm (25–34 weeks) neonates to compare the impact of facilitated tucking to routine care on the stress response (PIPP) during routine nursing assessments. 9/12 infants received a lower PIPP score with facilitated tucking, reflecting the fact that the stress during routine nursing assessment can be reduced by facilitated tucking
Corff et al. (1995) [84]	Randomized, crossover study in 30 preterm (25–35 weeks) neonates to compare the impact of facilitated tucking with routine care on vital signs and sleep disruption following heel lancing. A lower heart rate, a shorter crying time, and shorter sleep disruption times were documented during facilitated tucking
Cignacco et al. (2012) [85]	Randomized controlled trial in 71 (24–32 weeks) neonates to assess the effectiveness of sucrose, facilitated tucking, or both on the pain response following heel lancing, using the Bernese Pain Scale for Neonates. Facilitated tucking was less effective compared to sucrose, but combination of both interventions resulted in a further improvement in the recovery phase
Axelin et al. (2006) [86]	Prospective, randomized controlled trial in 20 preterm (24–33 weeks) neonates to assess the impact of facilitated tucking by parents on pain expression (Neonatal Infant Pain Scale, NIPS) and vital signs during endotracheal or pharyngeal suctioning. Facilitated tucking by parents resulted in a lower NIPS (median 3–5) score and the infant calmed down more quickly (median: 5–17 seconds)
Ward-Larson et al. (2004) [87]	Prospective, randomized crossover trial in 40 (23–32 weeks) preterm neonates to assess the impact of facilitated tucking (second nurse) to routine nursing on procedural pain (PIPP) related to endotracheal suctioning. PIPP scores during facilitated tucking were significantly lower compared to routine nursing care
Fearon et al. (1997) [88]	The responses of preterm neonates to swaddling after a heel lance were quantified in 15 preterm neonates after blood sampling. Preterm infants aged 31 weeks or older showed protracted behavioral disturbances that were reduced by the use of swaddling. In younger infants, there was a return to behavioral patterns irrespective of the treatment conditions
Marin Gabriel et al. (2013) [75]	NIPS scores in 136 healthy newborns. Skin-to-skin contact (SSC), combined with either sucrose (Sucr) of breastfeeding (BF) during heel prick. BF in addition to SSC provides superior analgesia to other kinds of non-pharmacological analgesia
Johnston et al. (2013) [89]	Therapeutic touch given immediately before and after heel lance in extreme preterm (<30 weeks) neonates in a randomized, blinded approach was ineffective (PIPP score) to reduce pain expression during and after heel lance
Alinejad-naeini et al. (2014) [90]	Crossover study on the behavioral pain (PIPP score) during endotracheal suctioning in 34 neonates (29–37 weeks). The incidence of severe pain was significantly lower (38.2–9%) when facilitated tucking was applied
Peyrovi et al. (2014) [91]	Crossover study on the behavioral pain (NIPS score) during endotracheal suctioning in 34 preterm neonates. There was no difference in pain scores, but the changes in heart rate were more blunted when facilitated tucking was applied
Gautheyrou et al. (2018) [92]	Facilitated tucking during early neonatologist-performed echocardiography in 50 very preterm neonates (26–29 weeks) was associated with lower pulmonary artery pressures, less heart rate variations, and improved the newborn comfort during the procedure
Perroteau et al. (2018) [93]	The add-on effect of facilitated tucking to non-nutritive sucking was assessed during and following heel lancing in 60 preterm neonates (28–32 weeks). There was no significant effect of facilitated tucking on pain scores (PIPP), but recovery was faster

scores and physiologic fluctuations and a faster return to baseline [80–93]. To test the comparative effectiveness of different non-pharmacological pain-relieving interventions, applied alone or in combination to document potential synergism, effectiveness of oral sucrose, facilitated tucking, or both, a prospective study in 71 preterm (24–32 gestational age) neonates was performed in 3 NICUs in Switzerland [85]. Facilitated tucking alone was significantly less effective in relieving repeated procedural pain than sucrose 24% (0.2 ml/kg). However, facilitated tucking in combination with sucrose had an added value in the recovery phase with lower pain scores compared to both single interventions [85].

Multisensorial Stimulation and Sensorial Saturation

Sensorial saturation is a multi-sensorial stimulation consisting of *simultaneous* delicate tactile, gustative, auditory, and visual stimuli. This procedure consists of simultaneously

attracting the infant's attention by massaging the infant's face; speaking to the infant gently, but firmly; and instilling a sweet solution on the infant's tongue. Non-painful stimulation, by engaging a number of channels (i.e., auditory, tactile, visual, olfactory, vestibular, gustatory), is thought to compete with the painful sensory input. In a systematic review on this topic, ten studies were retrieved that evaluated at least partial sensorial saturation [64]. Based on the evidence collected, the use of an oral solution alone is less effective than when combined with sensorial saturation, while sensorial stimulation without oral sweet solution is ineffective. Consequently, it was concluded that sensorial saturation can be used for all newborns undergoing blood samples or other minor painful procedures. It is more effective than oral sugar alone and promotes interaction between caregiver and infant [64, 75, 81, 85].

From Evidence to Practice: The Implementation Issue

Despite the available knowledge, deficits in the clinical management of pain remain. One reason is the gap between research evidence and translation of this knowledge into the clinical practice [94]. This is particularly true for non-pharmacological pain-relieving methods. Effective performance of some of these methods requires additional staffing and time. Although "facilitated tucking" is described as an efficient method with modest effect for acute pain relief, the clinical facilitators required to successfully implement such a resource consuming-intervention remain unclear. In essence, the costs and organizational constraints need to be balanced against possible (long-term) health gain benefits. A report on the limited compliance with pain management guidelines for heel blood sampling in European NICUs confirms this gap between available knowledge, guidelines, and bedside practices [95].

Another relevant question is how to integrate parents into these complementary interventions through either Kangaroo care or facilitated tucking. Kangaroo care is defined as holding the newborn skin-to-skin against the mother's body with or without additional covering and in an upright 40–60° angle. Kangaroo care was documented to have some effect on pain expression (PIPP score) during heel lancing [96]. Similar, skin-to-skin contact, containment, and maternal voice resulted in a reduction in duration of crying or grimacing during and following heel lancing. However, the Johnston study had a 40% refusal rate, indicating that not all parents are comfortable with these procedures and their contributions to the pain relief [96].

In two consecutive studies on parental facilitated tucking, Axelin et al. first illustrated that facilitated tucking by parents is indeed effective (NIPS score: 3 (2–6) versus 5 (2–7)) and safe in preterm neonates that undergo endotracheal suctioning [86]. This was followed by an evaluation of the parental willingness to actively participate in their preterm infants' pain care through parental facilitated tucking. The willingness to participate related to their internalized involvement, i.e., to what extent do the parents consider themselves skilled enough to take this responsibility [97].

Take-Home Messages

- Avoid procedural pain when possible, or at least, use the most appropriate technique [20, 21].
- Sucrose 24%, glucose 30%, or mother's milk, all respectively combined with a pacifier, are the most effective analgo-distractive techniques currently available for procedural pain relief in neonates. There is evidence in support of other non-pharmacological pain-relieving methods (e.g., swaddling, containment, multisensorial stimulation), mainly in synergism [72–74, 81, 85].
- The sweet solution should be administered on the tongue shortly before the initiation of the procedure. The illustration that this might not be as effective as anticipated should only enforce us to avoid procedural pain as much as possible [41].
- Do not overestimate the analgesic effect of these compounds, and do not misuse these compounds to perform "minor" surgical interventions when more appropriate analgo-sedatives (local or systemic) are needed [18, 19].

Pharmacological Interventions

Pharmacological interventions focus either on analgesia, sedation, or both. We will discuss agents commonly administered to attain analgesia with increasing potency (topical and local anesthesia, acetaminophen/paracetamol, morphine and fentanyl, remifentanil), followed by sedatives (benzodiazepines, chloral hydrate, propofol, dexmedetomidine) or both (ketamine, inhalational agents).

Topical and Local Anesthesia

Local anesthetics of the amide group (Ia) have effects on the central nervous system (depression or activation), peripheral nervous system (decreased conduction), and cardiovascular system (shortening action potential). Elimination is through primary renal elimination or through hepatic metabolic clearance. Hepatic metabolism does result in intermediate metabolites, and these metabolites have also been linked to some of the observed toxic side effects [98]. However, the extent of the metabolic clearance compared to the primary renal elimination in neonates is unknown. Besides analgesia, there is also an increasing experience with lidocaine to treat neonatal seizures. However, this specific indication is beyond the scope of this chapter. In essence, there remains a

delicate balance between effects and potential side effects in neonates with use of local anesthetics [98].

Topical local anesthetics are available in various forms such a lidocaine ointment or gel, and amethocaine/tetracaine cream, but EMLA as a cream, containing both 2.5% lidocaine and 2.5% prilocaine, is most commonly used and evaluated. We will first discuss efficacy data, followed by some observations on toxicity. In general, it provides good superficial (skin) anesthesia for 1–2 h when applied under an occlusive dressing. Application should be done about 1 h before the skin-breaking procedure.

In neonates, this has been evaluated for heel lancing, venipuncture, lumbar puncture, and circumcision, but data for skin-breaking procedures are to a certain extent conflicting (Table 18.3) [61, 99–109]. The latest meta-analysis on topical anesthesia for needle-related pain, when combining the available data on EMLA and amethocaine, studies reported a statistically significant reduction in pain compared to placebo during lumbar puncture (one study) and venipuncture (four studies), respectively, while it was clearly illustrated to be ineffective to reduce pain related to heel lancing [110]. For *venipuncture*, infants treated with EMLA had significantly lower heart rates and crying duration compared with infants treated with a placebo. However, oral sucrose 24% [111] or glucose 30% [112] in combination with a pacifier is more effective to reduce pain expression during venipuncture when compared to EMLA application. In infants, EMLA as mono-therapy only resulted in minimal benefits of pain related to venipuncture when compared to placebo [113]. However, the combination of sucrose and EMLA cream revealed a higher analgesic effect than sucrose 24% alone during venipuncture in preterm infants, so that this an argument for a multimodal approach [114].

Table 18.3 Reported papers on the analgesic effects of tetracaine/amethocaine in neonates (type of procedure highlighted) [61, 99–109]

Intramuscular injection	
Shah et al. (2008) [99]	Randomized, double-blind, placebo-controlled trial, *intramuscular injection* (vitamin K) in 110 term neonates, topical amethocaine gel 4%. There were no differences in crying duration, in pain score, and only the latency to cry was somewhat longer in the treated group. Topical amethocaine gel 4% was ineffective in reducing pain intramuscular injection of vitamin K in full-term neonates
Venipuncture	
Jain et al. (2000) [100]	Randomized, double-blind, placebo-controlled trial in 40 (pre)term neonates during *venipuncture*. Topical amethocaine provided effective pain relief (crying, neonatal facial coding system) during venipuncture in the newborn when used as single technique for analgesia
Lemyre et al. (2007) [101]	Randomized, double-blind, placebo-controlled trial in 142 preterm (from 24 weeks onwards) infants during *venipuncture*. Tetracaine did not significantly decrease procedural pain in infants undergoing a venipuncture, when used in combination with routine sucrose administration
Lemyre et al. (2006) [102]	Randomized, double-blind, placebo-controlled trial in 54 preterm neonates on the add-on effect of tetracaine gel in addition to sucrose to treat procedural pain related to *peripherally inserted central catheter (PICC) placement*. Tetracaine 4% when applied for 30 minutes was not beneficial in decreasing procedural pain associated with a PICC in very small infants
Larsson et al. (1998) [61]	120 term healthy newborns, *venipuncture for metabolic screening*, 0.5 g of EMLA or placebo on the dorsal part of the hand for 60 minutes, with NFCS and crying as outcome variables. NFCS and duration of crying significantly lower in the EMLA group
Long et al. (2003) [103]	Randomized, controlled trials 34 newborns (32–42 weeks), 15 exposed to tetracaine for *diagnostic venipuncture for metabolic screening or bilirubin*. NFCS and crying were assessed. Blunted pain reaction (low NFCS) in 14/15 of exposed, compared to 6/17 in the placebo group
Heel lancing	
Jain et al. (2001) [104]	Randomized, double-blind, placebo-controlled trial in 60 (pre)term neonates during *heel lancing blood sampling*. Topical amethocaine gel does not have a clinically important effect on the pain of heel prick blood sampling. Its use for this purpose cannot therefore be recommended
Bonetto et al. (2008) [105]	76 healthy term newborns, requiring heel lancing, comparing the effect of EMLA, oral paracetamol, or glucose 25% on *heel lancing-related* pain (neonatal infant pain score). The incidence of a NIPS score <4 was similar between placebo, paracetamol, and EMLA (47, 42 and 63%), while oral dextrose was most effective (84%, NNT 2.7)
Larsson et al. (1995) [106]	112 term healthy newborns, *heel lancing for metabolic screening*, 0.5 g of EMLA or placebo, with emphasis on the duration of the application (20, 30, 40, 50, 60, 90, or 120 minutes). No analgesic effect of EMLA was observed
Stevens et al. (1999) [107]	120 newborn preterm (30–36 weeks) neonates, EMLA 0.5 g compared to placebo, *heel lancing*, effect on premature infant profile PIPP score. Procedure 30 or 60 minutes after application. No differences in PIPP score, so not efficacious for pain relief
Lumbar puncture	
Kaur et al. (2003) [108]	60 newborns (>33 weeks), randomized controlled trial, *diagnostic lumbar puncture*. All newborns experienced pain, but EMLA vs placebo, EMLA attenuated the pain response (total behavioral score, heart rate), at insertion and withdrawal
Enad et al. (1995) [109]	EMLA did not reduce physiologic changes or behavioral pain scores in another randomized controlled trial in neonates (>34 weeks GA) undergoing lumbar puncture

Similar effects have been documented for pain relief during percutaneous venous catheter placement (heart rate, respiratory rate) and arterial puncture (behavioral pain score). For *lumbar puncture*, we are aware of two studies with conflicting results. Kaur et al. provided evidence that support the concept that EMLA is effective in reducing pain associated with needle insertion and withdrawal during lumbar puncture in newborn infants [108]. Unfortunately, compared with baseline observations, all newborn infants experienced pain as evidenced by increased heart rate, decreased oxygen saturation level, and total behavioral score [108]. In contrast, EMLA did not reduce physiologic changes or behavioral pain scores in another randomized controlled trial in neonates (>34 weeks GA) undergoing lumbar puncture [109]. Based on the available evidence, topical anesthetics may blunt the physiological markers of pain, but this does not result in a pain-free procedure [115].

Similar trends on limited to moderate effectiveness have been observed to treat pain during circumcision. EMLA cream (1–2 g) can be applied to the distal half of the penis with subsequent occlusive dressing, 60–90 minutes before circumcision is performed. However, a recent meta-analysis concluded that dorsal penile nerve block is significantly more effective as analgesia during circumcision when compared to EMLA [116]. Along the same line, a double-blinded randomized trial in 70 neonates comparing 3 multimodal analgesia strategies (EMLA + sucrose versus EMLA + dorsal penile nerve block versus EMLA + sucrose + ring block) documented that the last approach (EMLA + sucrose + ring block) was the most effective analgesic approach [117].

It is important to minimize systemic absorption by removing the cream just before the start of the surgical procedure. The first data on the efficacy and safety of this approach have been described by Taddio et al. [118]. Using a randomized approach, 38 neonates were treated with EMLA. Compared to 30 neonates in the placebo arm, neonates in the lidocaine-prilocaine group had less facial activity, spent less time crying, and had smaller increases in heart rate than the neonates in the placebo group. Blood methemoglobin concentrations (expressed as a percentage of the hemoglobin concentration) were similar (1.3%) in both groups. Lidocaine and prilocaine were detected in plasma in 61% and 55% of the infants treated with lidocaine-prilocaine cream, respectively. However, when compared to other regional analgesic interventions (ring block, dorsal penile block), the ring block was equally effective through all stages of the circumcision, whereas dorsal penile nerve block and EMLA were less effective during foreskin separation and incision, while methemoglobin levels were highest in the EMLA group, although not a single newborn required a specific intervention for these findings [119].

Pretreatment with EMLA decreases infant pain related to routine vaccinations, but the application of these data is limited to healthy infants, with a number needed to treat (avoid significant pain) of 3.7 [120, 121]. The combined use of EMLA and glucose 30% was proven to be effective when compared to placebo, while combining sucrose, oral tactile stimulation, and parental holding was also associated with significantly reduced crying in infants receiving multiple immunization injections [122]. However, the use of amethocaine has no effect on pain expression during intramuscular vitamin K administration in newborns [99, 121].

Besides EMLA cream, sprays (4% lidocaine, max 0.1 ml/kg) or gel (2%, max 0.3 ml/kg) for mucosal topical anesthesia (2) or local injection of lidocaine (up to 3 mg/kg max, equal to 0.3 of the 1% formulation) are also commonly used. Data in infants documented that nebulized lidocaine is not effective to reduce the pain response to nasogastric tube placement [123]. In contrast, lingual 24% sucrose is effective in reducing the behavioral and physiological pain response to nasogastric tube insertion in preterm infants [124]. We could not find data on the effects of mucosal spray to facilitate bronchoscopy or gastroscopy in neonates.

Besides the overall limited benefit or add-on effect of lidocaine, there is a relevant concern about toxicity in neonates. Different case reports and case series on the association of EMLA application and seizures or methemoglobinemia have been described. Newborns are at higher risk to develop methemoglobinemia because of reduced NADH-dependent methemoglobin reductase. The same limited effect/potential side effect balance can be constructed for tetracaine. In contrast, relevant methemoglobinemia was not documented as side effect in the earlier mentioned systematic review [110].

Take-Home Messages

- The overall evidence suggests at best a modest to moderate effect on procedural pain in neonates. This means that for most of the procedures, topical anesthesia should be considered as part of a multimodal analgesia [98].
- There remains a concern on absorption-related toxicity (seizures, methemoglobinemia). Maximal doses should be adhered to; absorption is more likely in the presence of disrupted skin. When applied for circumcision, EMLA should be removed just before the start of the surgical intervention [98].

Propofol

Propofol (2,6 di-isopropylphenol) is a highly lipophilic compound that exhibits rapid distribution from the blood to the subcutaneous fat and the central nervous system compartments with subsequent redistribution and metabolic clearance. It is considered to be a short-acting anesthetic (not an analgesic) that is rapid in its onset and short in duration after cessation [125]. Because of these pharmacokinetic

and dynamic characteristics, propofol became a frequently administered drug for induction and/or maintenance of anesthesia in children and, more recently, also in neonates. However, continuous administration may result in serious, sometimes lethal, metabolic complications ("propofol infusion syndrome") in children. This is of relevance, since it took about 15 years of unlicensed, off-label administration before this serious side effect and its risk factors in pediatric patients were recognized.

Because propofol is a water-insoluble phenolic compound, propofol clearance is exclusively by metabolic clearance. In adults, metabolism is mainly through glucuronidation. Since glucuronidation capacity in neonates displays important ontogeny, pharmacokinetics in this specific population are of utmost relevance. Data on propofol pharmacokinetics in neonates are available [126]. Standardized propofol clearance at 38 weeks postmenstrual age (PMA) (CL_{std}) was 0.029 l/min. A fixed value in neonates with a postnatal age of ≥10 days further improved the model and resulted in the equation (CL_{std} . (PMA/38)11.5 + 0.03) l/min for neonates ≥10 days. When compared to adults (1.91 l/min) following an intravenous bolus, the difference in clearance is impressive (65-fold) [126]. The complex interplay between size and maturation results in an overall low propofol clearance capacity at birth (estimated to be 0.029 l/min at 38 weeks postmenstrual age) with a subsequent postnatal (PNA) and postmenstrual age (PMA)-related increase. Consequently, both preterm and term neonates in the first week of postnatal life have an increased risk for accumulation following intermittent bolus or continuous administration of propofol due to the reduced clearing capacity. Secondly, there is still extensive unexplained variability in neonates after introducing PMA and PNA as covariates, making exposure predictions in neonates more difficult [126].

Pharmacodynamics of propofol have been described, with specific emphasis on the (side) effects of propofol during endotracheal intubation (Table 18.4) [127–135]. Ghanta et al. reported on propofol (2.5 mg/kg) pharmacodynamics

Table 18.4 Summary of the prospective studies on the use of propofol to facilitate endotracheal intubation in (pre)term neonates, reflecting the variability in clinical characteristics, outcome criteria, co-medication, and doses evaluated in the different studies [127–135]

Reference	Study design and results
Welzing et al. (2011) [127]	Prospective, observational study on intubating conditions, vital signs, extubation times, and outcome in 13 preterm neonates treated with propofol (1 mg/kg) for an INSURE (*in*tubation, *sur*factant, *e*xtubation) procedure. The study was stopped early because of significant cardiovascular side effects expressed as distinct drop in mean blood pressure (mean values = 38 mmHg to 24 mmHg 10 minutes after propofol exposure). Intubation conditions were reported to be good
Nauta et al. (2011) [128]	Retrospective analysis on trends in arterial blood pressure (invasive) in 21 preterm neonates (28.8, SD 3.5 weeks) exposed to propofol (2 mg/kg), 5/21 co-treated with atropine. The decline in mean arterial blood pressure before and after propofol administration (48–41 mmHg) was not significant, and the proportion of patients with hypotension was similar before and after propofol exposure
Ghanta et al. (2007) [129]	Randomized, open-label controlled trial comparing propofol (2.5 mg/kg) with morphine (100 μg/kg)-atropine (10 μg/kg)-suxamethonium (2 mg/kg) as induction agents for endotracheal intubation in 63 preterm neonates. There were no differences in vital signs but through oxygen saturation was significantly lower in the M-A-S group, and recovery time was shorter in the propofol group (recovery time = return of spontaneous muscle movement)
Papoff et al. (2007) [130]	Pilot study in 21 (pre)term neonates with severe respiratory distress syndrome. Fentanyl (1.5 μg/kg) was co-administered with propofol (2 mg/kg over 20 seconds), and propofol was administered a second time if more than 1 attempt to intubate was needed. A subscore of ≤2 for all items of the Helbo-Hansen score system was qualified to reflect an easy intubation. Intubation was qualified as easy in all cases, intubation at first attempt in 18/21. Oxygen desaturation (all >60%) was documented in 7/21 cases. These desaturation events were commonly associated with a transient decrease in systemic blood pressure (treated with cristalloids, 10 ml/kg)
Penido et al. (2011) [131]	Double-blinded, randomized controlled trial in 20 preterm (28–34 weeks) neonates, exposed to either propofol (2 mg/kg) or midazolam (0.2 mg/kg). Both (propofol/midazolam) were combined with remifentanil (1 μg/kg). No differences in intubation conditions or number of attempts needed were observed
Simons et al. (2013) [132]	Prospective study in 62 procedures (24–49 weeks postmenstrual age), with propofol to facilitate endotracheal intubation. The mean dose was 3.3 (SD 1.2) mg/kg, with hypotension in 39% of the cases, and the use of other drugs in 15% of the procedures.
Smits et al. (2016) [133]	Propofol dose seeking study in 50 neonates that had to undergo either endotracheal intubation or INSURE. Propofol effective dose for 50% for preterm neonates <10 days of age varied between 0.7 and 1.5 mg/kg. These "low" doses were sufficient to sedate, but were associated with permissive hypotension
Durrmeyer et al. (2018) [134]	Randomized controlled trial in 171 neonates (mean gestational age 30.6 weeks) received either atropine-propofol (n = 89) or atropine-atracurium-sufentanil (n = 82) as premedication for a non-emergency neonatal intubation. There were no significant differences (primary: prolonged desaturation) between both groups, with adverse events observed in 11% vs 20% of the cases
Dekker et al. (2019) [135]	Randomized controlled trial in 78 preterm neonates (26–36 weeks) that underwent minimal invasive surfactant therapy (MIST). COMFORT-neo score <14 was more common in the propofol (1 mg/kg) exposed group, but the incidence of desaturation and the need for nasal intermittent mandatory ventilation were also more common. There were no differences in the incidence of hypotension, bradycardia, intubation, or pneumothoraces

in 33 preterm neonates during semi-elective endotracheal intubation. Compared to a morphine/atropine/suxamethonium regimen, time until sleep, muscle relaxation, and time to achieve successful intubation were shorter [127]. These short-acting, sedative effects were confirmed by others [128–135]. In contrast however, a significant impact on blood pressure (decrease 20%) and oxygenation have been reported in term neonates, in neonates with an associated cardiopathy and in two cohorts of preterm neonates undergoing chest tube removal ($n = 20$, 3 mg/kg) or during INSURE ($n = 13$, 1 mg/kg). We hereby would like to remind the readers that there is an association between fluctuations in blood pressure and intracranial hemorrhage in the first days of postnatal life in preterm neonates [136]. Propofol also affects the myocardial function in newborns, in part depending on the formulation administered [137]. Drug-related hypotension and decreased cerebral activity after intubation with low propofol doses in preterm neonates have been observed, without evidence of cerebral ischemic hypoxia, while cerebral autoregulation remained intact during propofol-related hypotension in almost all (95%) the events [138]. Because spontaneous respiration can be maintained, propofol (intermittent bolus, 1 mg/kg, combined with topical anesthesia) has been used to facilitate diagnostic or therapeutic bronchoscopies. This approach is similar as in children, but reports in neonates are still limited to case reports. The use of a continuous positive airway pressure mask and maintaining spontaneous breathing significantly reduces the risk of relevant oxygen desaturation during the procedure. Along the same line, there is a report on the combined use of propofol + fentanyl, combined with laryngeal mask ventilation to facilitate laser photocoagulation for retinal surgery [139].

Continuous administration of propofol has been used to facilitate procedural sedation during imaging procedures in neonates, and a manual propofol infusion regimen for neonates and infants has been suggested, but has not yet been validated [140]. Taking the abovementioned covariates (postnatal and postmenstrual age) of propofol pharmacokinetics and the prolonged scanning times into account, we suggest to remain cautious with prolonged propofol infusions in neonates. We are aware of two cases of "propofol infusion syndrome." Sammartino reported on the clinical and metabolic symptoms of "propofol infusion syndrome" in a preterm neonate, while another term newborn (postnatal day 7, lung surgery) developed this syndrome following a single dose of propofol (10 mg, 3 kg) administration [141, 142].

In the absence of integrated PK-PD models in neonates, we can only speculate on the target propofol concentration to aim for in neonates [143]. However, when we take the available pharmacokinetic estimates in early life into account, accumulation may occur even at "routine adult or pediatric" doses in early neonatal life. Although propofol seems to be a promising compound for versatile short-acting analgo-sedation, dose findings and safety studies are urgently needed. In a Cochrane review, Shah et al. concluded that no practice recommendation could be made based on the available evidence regarding the use of propofol in neonates [144]. At present, a relatively safe dose range has been identified to conduct randomized controlled and comparative trials to further assess the safety and efficacy of propofol.

Take-Home Messages

- There is extensive variability in propofol clearance within the neonatal population, in part explained by both postnatal and postmenstrual age [126, 143].
- A manual propofol infusion regimen for neonates and infants has been suggested [140].
- There is conflicting information on the magnitude of hemodynamic (side) effects of propofol in (pre)term neonates [129, 136].
- There is experience with intravenous bolus propofol administration to facilitate endotracheal intubation, but there is important variability in clinical characteristics, outcome criteria, co-medication, and doses evaluated in the different studies [127–135].
- We do not recommend the use of propofol for sedation in ventilated neonates.

Ketamine

Ketamine is an anesthetic agent that provides amnesia, sedation, and analgesia. It can be administered by intravenous, intramuscular, nasal, rectal, or oral route with a systemic bioavailability of 93%, 50%, 25%, and 17%, respectively. It has an established role in pediatric anesthesia and is routinely used for induction and maintenance of anesthesia. This is in part due to the fast onset (30–60 seconds) and short duration of action, with limited hemodynamic and respiratory effects. The analgo-sedative effects are mediated through different mechanisms and contain both peripheral and central site effects. The contribution of N-methyl-D-aspartate (NMDA) receptor antagonism and interaction with cholinergic, adrenergic, serotonergic, opioid pathways, and local anesthetic effects remains to be fully elucidated. Hypersalivation is commonly observed during ketamine administration, resulting in the clinical practice to co-administer atropine or another anti-sialagogue. Ketamine is rarely used as a single anesthetic agent, is more commonly used as part of a multimodal anesthesia strategy, but can be considered for procedural analgo-sedation [145, 146]. The cardiovascular stability observed with ketamine has made it a popular induction agent in infants with a congenital cardiopathy. In contrast, raised intracranial or intraocular pressure may be contraindications for ketamine analgo-sedation.

Pharmacokinetics

Ketamine is a highly lipid-soluble drug with rapid distribution from the systemic circulation to the brain. Due to these characteristics, systemic absorption of caudally or epidural injected ketamine is also more likely [147]. It is a racemic (50/50) mixture of two enantiomers, and the S(+) enantiomer is four times more potent compared to the R(−) enantiomer. Ketamine undergoes N-demethylation to norketamine. This metabolite has limited analgo-sedative effects (30% of the parent compound). Plasma protein binding is limited (47%), and the metabolic clearance strongly relates to the hepatic blood flow with a high extraction ratio. Ketamine displays extensive first-pass drug metabolism, explaining the much higher doses suggested for oral as compared to intravenous administration, while rectal administration results in less predictable exposure. Consequently – when corrected for allometric differences – clearance in children and infants is similar to adults, but reduced (80–26 l/h/70 kg) in neonates [148]. In a randomized, crossover, trial to assess the effects of ketamine on pain expression during endotracheal suctioning in 16 preterm neonates, plasma ketamine concentrations 15 minutes after intravenous administration (0.5, 1 or 2 mg/kg compared to placebo) were 103 (range 73–134), 189 (144–235) and 379 (320–437) ng/ml, respectively. Unfortunately, norketamine data were not collected, and sampling was limited to the 15 minutes time point [146]. The earlier discussed PK ketamine data explains that the dosing suggestions for analgo-sedation in neonates (0.5–1 mg/kg) are lower when compared to older children and much higher for oral as compared to intravenous administration (2–5 mg/kg oral).

Pharmacodynamics

The number of observations on effectiveness and safety of ketamine in neonates is limited. In the earlier mentioned study of Saarenmaa et al., these authors evaluated the ketamine-related pain relief in an endotracheal suctioning model in 16 preterm (31, SD 3 weeks) neonates. The increase in heart rate, arterial blood pressure, and plasma catecholamines in response to endotracheal suctioning was not blunted when different (0.5, 1 and 2 mg/kg) doses of ketamine were compared to the response after placebo [146].

Combined with atropine, the effects of ketamine (0.5 mg/kg increments) to facilitate LISA were prospectively assessed in 29 preterm neonates. This resulted in low pain scores and stable hemodynamics (blood pressure and heart rate transiently increased) while prolonged desaturations (17/29, 59% saturations <80% for at least 60 seconds) and apnea necessitating intubation in 7 (24%) cases [149]. In a randomized controlled trial in 60 neonates that had to undergo neonatal intubation in the delivery room, nasal midazolam (0.2 mg/kg) versus nasal ketamine (2 mg/kg) resulted in similar hemodynamic and respiratory effects, but nasal midazolam was more effective as sedative (higher success rate 89 versus 58%; shorter time until intubation, 10 versus 16 minutes) to facilitate intubation [150].

Another dataset relates to the use of ketamine sedation during the treatment of retinopathy of prematurity. In a NICU ward setting, ketamine sedation allowed laser therapy for retinopathy of prematurity in 11 preterm neonates (14 procedures). An empirical initial intravenous dose of 0.5 mg/kg was given, followed by further increments every 2 minutes if the child became distressed at insertion of the speculum. The median total dose was 2.4 mg/kg, the median duration of the intervention 1.6 h. Atropine was co-administered to minimize the salivation effect and to blunt reflex bradycardia [153]. Ulgey et al. reported on their experience with ketamine (1 mg/kg, followed by 0.25 mg/kg/h, combined with propofol, 1 mg/kg, followed by 0.1–0.15 mg/kg/min) in 30 preterm neonates who underwent retinal surgery. Compared to historical controls, blood pressure and heart rates were similar, but only 2/30 versus 11/30 (6 versus 36%) neonates needed postoperative ventilation [152].

We would also like to mention a single case report of a newborn with epidermolysis bullosa. Oral ketamine was used in this patient to facilitate dressing changes. Over 4 days, the dose was titrated from 0.125 to 0.75 mg/kg and resulted in sufficient sedation within 15 minutes after administration and dressing changes without crying or resisting for 45 minutes [153]. We hereby would like to mention that this oral dose is lower compared to the oral dosing suggested. In our opinion, differences in intestinal permeability support the need for dosing individualization.

Finally, there is growing concern about ketamine causing dose and duration-related neuronal apoptosis in animal (mice, rat, rhesus monkey) experimental studies soon after birth. At present, it is unclear to what extent this also applies to human neonates and infants. Moreover, similar animal experimental observations have been reported for other analgo-sedatives (e.g., opioids, benzodiazepines, propofol, inhalational agents). Related to safety, there is a small prospective cohort of 51 former preterm newborns that were exposed to ketamine to facilitate tracheal intubation. Compared to control and reference data, there were no differences in neurological development at the age of 1 and 2 years [154].

Take-Home Messages

- Ketamine is rarely used as a single anesthetic agent, but is more commonly used as part of a multimodal anesthesia strategy.
- The clinical experience with ketamine in neonates is accumulating, but still limited.

- There is a concern about ketamine causing dose and duration-related neuronal apoptosis in animal (mice, rat, rhesus monkey) experimental studies soon after birth [6–10]. The available safety data are still very limited.

Remifentanil

Besides morphine and fentanyl, there are also observations on shorter-acting opioids in neonates. Alfentanil, sufentanil, or more recently remifentanil have been used mainly for short procedures such as endotracheal intubation, retinal laser surgery, or central catheter placement, while there is anecdotal experience during major surgery and to maintain analgo-sedation during mechanical ventilation [16, 125]. Remifentanil hydrochloride is a short-acting, μ-receptor opioid agonist. It achieves its peak analgesic effect within a minute of administration, 3–4 times faster when compared to fentanyl and much more fast when compared to morphine. Its effect also disappears fast after infusion has been stopped. This is also the case in neonates, since remifentanil is metabolized by plasma and tissue esterases, and these enzymes are already at an adult level of activity in early life [155].

Table 18.5 provides a summary of the available studies on endotracheal intubation with remifentanil in neonates [156–164]. These studies do reflect the difference between the reported studies on remifentanil to facilitate endotracheal intubation in (pre)term neonates. There is variability in clinical characteristics (preterm or term, INSURE or ventilation), outcome criteria (intubation score, duration of the procedure, physiological variables), co-medication, and doses (1–4 μg/kg intravenous slow bolus) evaluated. Based on the cumulative prospective and retrospective evidence reported in about 250 cases exposed to remifentanil (Table 18.5), despite its good pharmacokinetic profile, it fails as mono-drug to attain effective sedation to facilitate intubation and has been associated with a relevant minority of cases with chest rigidity (4–42%).

Table 18.5 Summary of the reported studies on remifentanil to facilitate endotracheal intubation in (pre)term neonates, reflecting the variability in clinical characteristics, outcome criteria, co-medication, and doses (1–4 μg/kg, dose highlighted) evaluated [156–164]

Reference	Study design and results
Norman et al. (2011) [156]	Randomized controlled trial in 34 preterm (<37 weeks) neonates for semi-urgent intubation. Atropine/morphine compared to RSI [rapid sequence intubation, based on glycopyrrolate, thiopental, suxamethonium and remifentanil (*1 μg/kg*)]. Primary outcome: intubation score ≤10, secondary outcomes: procedural duration, physiological/biochemical variables, aEEG, pain scores. Intubation score was superior in the RSI group [5 (IQR 5–6) compared to 12 (IQR 10–13.5)). Plasma cortisol and pain scores were similar, but fluctuations in physiological variables were more pronounced and prolonged in the morphine group
Choong et al. (2010) [157]	Double-blind, randomized controlled trial, 30 (pre)term neonates, semi-elective intubation. Remifentanil (*3 μg/kg*) compared to fentanyl (2 μg /kg) and succinylcholine (2 mg/kg). Primary outcome: time to successful intubation. Secondary outcomes: physiological variables, adverse events, survey on intubation conditions, and time until return of spontaneous respiration. There were no differences in time to successful intubation (156/247 seconds). Premedication with remifentanil attenuated physiologic responses during intubation comparable to fentanyl and succinylcholine in neonates. Intubation conditions were rated more favorably with fentanyl/succinylcholine. Muscular rigidity was observed in the remifentanil group (n = 2/15)
Welzing et al. (2009) [158]	Prospective, descriptive pilot study in 21 preterm (29–31 weeks) neonates receiving remifentanil (*2 μg/kg*, combined with atropine, 10 μg/kg) as induction agent for the INSURE (intubation-surfactant-extubation) procedure. Outcome variables were intubation conditions, time until extubation, and complications. Intubation conditions were qualified as excellent or good. Average extubation time after surfactant administration was 16.9 (1–45 minutes), followed by a mean of 3.3 (1–8) days of respiratory support (CPAP)
Pereira e Silva et al. (2007) [159]	Double-blind randomized controlled trial in 20 preterm (28–34 weeks) neonates to evaluate intubation conditions following either morphine (150 μg/kg) or remifentanil (*1 μg/kg*), both combined with midazolam (0.2 mg/kg). Overall intubation conditions were better in the remifentanil group
Hume-Smith et al. (2010) [160]	Remifentanil dose seeking study (sequential up-and-down design), including 20 neonates and young infants (0–<4 months, mean weight 5.9 kg). the ED_{50} was *3.1–3.7 μg/kg* when remifentanil was co-administered with glycopyrrolate (10 μg/kg) and propofol (5 mg/kg)
Avino et al. (2014) [161]	Comparison between remifentanil (n = 36, 1 μg/kg) and morphine (100 μg/kg) + midazolam (50 μg/kg) (n = 35). No significant differences in efficacy (intubation conditions poor first attempt 25 vs 28.8%, 28.6 vs 10% at second attempt) and neither in side effects (including hypotension, bradycardia)
De Kort et al. (2017) [162]	Prospective, single-center study in preterm that needed intubation for INSURE. Titrated administration (*1 μg/kg, can be repeated 3 times*). Early termination after inclusion of 14 preterms. Adequate sedation was only achieved in 2/14, chest wall rigidity was observed in 6/14, and additional propofol was administered in 6/14 cases
Audil et al. (2018) [163]	Retrospective chart review, compared to historical morphine data in 30 cases, limited data on intubation conditions. Extubation was more successful in the 65 remifentanil (*2 μg/kg, slow infusion 1–2 minutes*), cases (88 vs 33%), chest wall rigidity reported in 4% of remifentanil cases
Chollat et al. (2019) [164]	Retrospective study, remifentanil (*0.5–0.1 μg/kg/min as continuous infusion*) + atropine (10 μg/kg) in 54 neonates. Throughout the time interval, the remifentanil dose has been reduced twice in an attempt to limit the side effects. Successful first intubation 33%; chest wall rigidity 11%; bradycardia 23%; desaturation 37%

Data on a dose-response for remifentanil to facilitate endotracheal intubation have been reported. Based on observations in 32 "term neonates," it was documented that the effective remifentanil dose in 50% and 98% (ED_{50} = 1.7, SD 0.1 μg/kg, and ED_{98} = 2.88, SD 0.5 μg/kg) were similar between "neonates" (mean weight 8 kg, SD 2.2) and children [165]. However, this remifentanil dose was part of a multimodal anesthesia in combination with propofol (4 mg/kg), and glycopyrrolate (10 μg/kg) and the "neonates" were in fact infants (mean age 7 months, SD 3.3). In another dose-response study with sequential up-and-down design, 20 neonates and young infants (0–<4 months, mean weight 5.9 kg), the ED_{50} was significantly higher (3.1–3.7 μg/kg) when remifentanil was co-administered with propofol (5 mg/kg) and glycopyrrolate (10 μg/kg) [165]. In preterm neonates, Chollat et al. also reported on their experience using a dose de-escalation approach to avoid side effects during intubation, but with relevant failure on efficacy, irrespective of the dose [166].

In summary, remifentanil remains a promising compound, still in search of its indications in neonates [167]. To assess the analgesic and procedural efficacy of low-dose remifentanil infusion during percutaneous central catheter placement in preterm infants, 54 preterm neonates were randomly assigned to remifentanil infusion (0.03 μg/kg/min) or placebo in addition to 0.3 ml of 12% sucrose (oral) combined with non-nutritive sucking. Pain (PIPP) scores were significantly lower in neonates exposed to remifentanil, suggesting better pain and distress control without significant difference in the time to complete the procedure and in the number of attempts needed [168]. Sammartino et al. reported on their experience with remifentanil (0.75–1 μg/kg/min at start, 3–5 μg/kg/min during procedure) combined with intravenous midazolam (0.2 mg/kg) for retinal laser therapy in six preterm neonates [169]. The same group also reported on two cases of babies born at 26 weeks' and 27 weeks' gestation, weighing 580 g and 400 g, respectively, undergoing laparotomy for necrotizing enterocolitis [170]. Both received a midazolam bolus and continuous remifentanil infusion. Finally, this group also reported on their experience with remifentanil for analgo-sedation during mechanical ventilation. In their hands, remifentanil provided adequate analgesia, with a significant reduction of NIPS and COMFORT score since 1 h after starting the infusion of remifentanil [171]. The drug was initially administered at a dose of 0.075 μg/kg/min, but in 73% of newborns, the latter had to be increased up to a dose of 0.094 (SD 0.03) μg/kg/min. Using this dose, 97% of the newborns were assessed and classified as having adequate analgesia and sedation. The time elapsed between the discontinuation of remifentanil infusion and extubation was 36 (SD 12) min, reflecting its short-acting character [171].

However, in the clinical setting, this short-acting and versatile characteristics needs further considerations. A specific advantage of remifentanil is that this compound undergoes metabolic clearance by plasma esterases, resulting in fast and predictable clearance, irrespective of liver or renal function. Consequently, the analgo-sedative effects disappear very soon after discontinuation of remifentanil since the drug is cleared very rapidly. This is perfect or optimal when used for procedural analgo-sedation without subsequent pain. However, the "short-acting" concept hereby refers to both its onset of action and end of action: remifentanil-related analgo-sedation disappears very soon after discontinuation. This warrants anticipation and its management may be dependent on the indication [172].

When used for major surgery, anticipation and replacement by another (longer) acting opioid or non-opioid analgesic is needed, or the remifentanil infusion should be prolonged. Further continuation will however more likely result in potential negative effects such as opioid-induced tolerance or hyperalgesia since these phenomena are much more common when opioids with a short elimination half-life are administered [172]. The remifentanil-based analgesia and sedation of pediatric intensive care patients (RAPIP) trial examined whether remifentanil induced tolerance, withdrawal, or hyperalgesia compared to fentanyl (11 and 12 cases respectively) in neonates. A randomized controlled trial of intubated neonates compared the efficacy and safety of a remifentanil to fentanyl-based sedation regimen. When administered for less than 96 h, remifentanil did not increase the risk of tolerance, withdrawal, or opioid-induced hyperalgesia [172].

Take-Home Messages

- Remifentanil is a very short-acting compound with accumulating experience in neonates [16, 167].
- Its pharmacological profile seems suited for short procedural analgo-sedation, e.g., INSURE procedure, although mono-therapy commonly results in side effects like chest rigidity (Table 18.5) [156–164].
- Good predictability, fast onset, and subsequent fast disappearance are suggested to be advantageous. Clinicians need to be aware of potential fast-appearing tolerance, the phenomenon of hyperalgesia, and the potential risk of chest rigidity.
- When administered to 11 ventilated neonates for less than 96 h, remifentanil did not increase the risk of tolerance, withdrawal, or opioid-induced hyperalgesia compared to fentanyl [172].

Chloral Hydrate

Chloral hydrate is still widely used as (short) term sedative and hypnotic, but has no analgesic activity. In early infancy, indications commonly considered are procedural sedation

for non-painful or noninvasive examinations (like echocardiography, imaging techniques, hearing evaluation) or non-specific syndromes like insomnia or non-opioid withdrawal syndrome. A recent analysis on Canadian sedative use in NICU ventilated preterm neonates (<35 weeks) suggests that the use of sedatives for more than 24 h in this setting is low (16% of 5638 ventilated preterm neonates). However, in exposed cases, choral hydrate (44.2%) was commonly used, only marginally lower compared to phenobarbital (44.9%), followed by midazolam (37.9%), lorazepam (12.9%), ketamine (1.4%), or propofol (0.2%) [173].

Chloral hydrate can be administered by oral or rectal route. Following oral administration, absorption is rapid with subsequent hepatic metabolism to trichloroacetic acid or trichloro-ethanol (TCE). TCE subsequently undergoes conjugation and renal elimination. The TCE metabolite also has sedative effects, and because its elimination is delayed – most prominent in early life (elimination half-life is about 10 h in toddlers, but up to >50 h in preterm neonates) – accumulation and subsequent sedation may result from this metabolite [174, 175]. Preterm neonates and/or neonates with impaired renal or hepatic elimination are at an increased risk. Prolonged exposure may also result in gastritis, nausea, and/or vomiting; overt overdosing or accumulation may also result in arrhythmia [176]. Finally, there is a concern that chloral hydrate may have genotoxic effects. To illustrate this, sister chromatid exchange and micronucleus frequencies were determined in lymphocytes of infants before and after chloral hydrate exposure. After treatment, the frequencies of sister chromatid exchange and micronuclei were significantly increased, suggesting that chloral hydrate has moderate genotoxic potential [177]. Because of all these side effects, prolonged repeated administration of chloral hydrate should be avoided. However, this practice is rather common. In a recent audit from the Melbourne NICU, a total of 238 doses were administered to a cohort of 32 neonates, reflecting the common practice of repeated administration [178]. However, this does not mean that single-dose administration is without any risk.

The usual dose is 20–70 mg/kg by oral, nasogastric, or rectal route, with a tendency to go for relatively higher doses for rectal administration. Subsequent sedation can be anticipated within 30–45 minutes. Sedation may be prolonged, most common in preterm neonates because of the delayed TCE clearance. To further illustrate this, we refer to a study on the pharmacodynamics of chloral hydrate in 26 former preterm infants at term age. Sedation (COMFORT), feeding behavior, and cardiorespiratory events (bradycardic events, apneas) before and after administration of chloral hydrate (oral, 30 mg/kg) were prospectively evaluated in former preterm infants, exposed to chloral hydrate to facilitate hearing screening [179]. A significant increase in sedation up to 12 h after administration and a minor but significant decrease in oral intake (161–156 ml/kg/day) were observed. Moreover, a significant increase in the number of bradycardic events and in the duration of the most severe bradycardic events was observed. Infants who displayed severe bradycardic (<60/min) events (n = 13) after administration of chloral hydrate had a lower gestational age at birth. Based on the methodology (cardiorespiratory monitoring) applied, the study cannot discriminate between central and obstructive apnea [179].

Chloral hydrate-related sedation may result in central hypoventilation or apnea. Due to reduction in muscular tone and hypotonia of the upper airway maintaining muscles, obstructive apnea has also been described. In animal experimental setting, there was a significant decrease in electromyographic activity of the mouth floor muscles compared to the diaphragmatic muscle following chloral hydrate exposure [180, 181]. This may result in obstructive apnea, more common in infants or young children with obstructive apnea syndrome, or in neonates with malformations or micro/retrognatia. Obstructive apnea with secondary bradycardic episodes has been observed in young infants exposed to chloral hydrate to facilitate echocardiography [182].

Case reports on the association of chloral hydrate exposure and sudden infant death syndrome have also been described. Since chloral hydrate – in part due to the TCE metabolite – is a long-acting compound, events may occur hours following the procedure. Once again, it seems that (pre)term neonates are more vulnerable to display relevant bradycardic events up to 24 h after exposure [179].

There are studies that reported on the efficacy and complications of chloral hydrate sedation, but these studies do not always report on the subgroup of (pre)term neonates in the first month(s) of life. Litman et al. reported on efficacy and complications following chloral hydrate (50–75 mg/kg) exposure to facilitate MRI examination in 1394 infants [176]. Oxygen desaturation was more likely in hospitalized patients, in patients with a lower weight during drug administration, those who had a higher American Society of Anesthesia (ASA) status and those who were younger (both related to postnatal as well as postmenstrual age). The incidence of desaturation (<90%) or the need for supplemental oxygen was approximately 20% in term and preterm infants. There were ten episodes of bradycardia in eight infants, six of whom were preterm. The predicted probability of post-procedural oxygen desaturation in early neonatal life is higher in preterm (0.1) compared to term neonates (0.05), with subsequent less decrease in predicted probability (at the postnatal age of 100 days = 0.035 as compared to 0.015) [176]. Heistein et al. reported on their experience with chloral hydrate (80 mg/kg, oral) to facilitate pediatric echocardiography, including 58 neonates and 398 young (1–6 months) infants. There was a moderate decrease in heart rate and blood pressure, while adverse events were observed in 10.8% (apnea (n = 3), airway obstruction (n = 15), hypoxia

(*n* = 65), hypercarbia (*n* = 40), hypotension with poor perfusion (*n* = 4), vomiting (*n* = 4), and prolonged sedation (*n* = 36)). Adverse events were more common in infants <6 months [182].

The (side) effect profile of chloral hydrate has also been compared with other non-pharmacological and pharmacological techniques. The effect of fasting practice on sedation with chloral hydrate has been evaluated by Keidan et al. by comparing two different practices in two different hospitals for auditory brainstem response in neonates [183]. Fasting was associated with an increased failure rate of initial sedation. As a consequence, a higher total dose of chloral hydrate was required in the fasting group, also resulting in prolonged post-procedural sedation [183]. In contrast, compared to a "feed-and-scan" approach alone, chloral hydrate (50 mg/kg, oral or rectal) resulted in a shorter time until scanning and shorter scanning duration in 25 neonates, but no data on the post scanning recovery were provided [184]. In essence, it is reasonable to conclude that a combined or stepwise approach (feeding and chloral hydrate or feeding followed by chloral hydrate when needed) seems to be the best approach [185]. Such a "feed and wrap" strategy to facilitate imaging has also been reported in 47 neonates with initial successful imaging in 42/47 cases, resulting in only 5 neonates exposed to chloral hydrate [186]. In a recent UK survey, chloral hydrate was the most commonly used sedative (42/47, 89%) in units that either routinely or "as needed" used sedation (47/53) as part of the combined practice of "feed and wrap + sedative" [187]. We hereby re-illustrate the add-on value of complementary interventions to reduce the exposure to analgo-sedatives or to improve the effectiveness of a pharmacological intervention.

Finally, there are some important comparative studies. Oral pentobarbital (4 mg/kg) was compared to choral hydrate (50 mg/kg) for sedation in infants (<1 year) during neuroimaging. Based on observations collected in 1316 infants, there was no difference in effectiveness, in time to sedation, and in time to discharge, but the overall adverse event rate was lower with pentobarbital (0.5%) than with chloral hydrate (2.7%) [188]. Unfortunately, data in the subgroup of neonates were not reported. In contrast, chloral hydrate (75 mg/kg) was more effective and had similar side effects when compared to midazolam (0.2 mg/kg intravenous) in a crossover study in seven term neonates [189]. Miller et al. reported on a comparative study with dexmedetomidine (2 or 3 μg/kg, intranasal) versus choral hydrate (70 mg/kg, oral) sedation for transthoracic echocardiography in 150 infants (<3 years). All cohorts displayed a similar decrease in heart rate (22% reduction for chloral hydrate, and a similar discharge time (80–90 minutes), with similar efficacy [190].

Take-Home Messages

- Single-dose administration of chloral hydrate is a commonly used approach to facilitate non-painful procedural sedation, but focused studies in (pre)term neonates are limited.
- Initial sedation can be anticipated after 15–30 minutes. There is less certainty about the duration of this sedation, but sedative effects in neonates have been described up to 24 h afterwards [174, 175, 179].
- It is reasonable to monitor (pre)term neonates to at least the equivalent of 46 weeks postmenstrual age after chloral hydrate exposure [179].
- A genotoxic risk has been linked to chloral hydrate exposure [177].

Morphine and Fentanyl

In the Pediatrix reports on NICU drug use, morphine and fentanyl are in the top 30 list (19 and 25/30) of drugs prescribed to neonates, with an estimated exposure of 56 and 35/1000 admitted neonates in the 1997–2004 cohort, to increase to positions 7 and 14 with an estimated exposure of 70 and 51/1000 admitted neonates, with appearance of paracetamol on position 16 with 43/1000 in the more recent (2005–2010) analysis [191, 192]. These compounds are hereby the most commonly administered analgesics to NICU patients.

Morphine hereby probably is the most extensive evaluated analgesic in neonates and can be administered by oral (bioavailability is about 30%) or intravenous route. Morphine is a narcotic analgesic that stimulates opioid receptors, both within and outside the central nervous system. This explains effects (sedation, analgesia, miosis) and side effects (bladder retention, paralytic ileus, respiratory depression). It also necessitates appropriate monitoring (cardiorespiratory, sedation) during and following morphine exposure. It has been suggested that pain relief necessitates a morphine level of 120 ng/ml, while adverse effects appear at levels >300 ng/ml [193]. These levels are different in neonates, very likely due to both differences in opioid receptor expression/activity, maturational phenotypic glucuronidation activity, but likely also because of differences in transporter activity at the level of the blood-brain barrier [194]. Morphine is converted to two glucuronide metabolites (morphine-3-glucuronide and morphine-6-glucuronide), and these metabolites subsequently are eliminated by renal route. While morphine-3-glucuronide is an antagonist to the effects of morphine, morphine-6-glucuronide also has analgesic and respiratory depressant effect. Morphine sulfation is only a very minor metabolic pathway [195].

Despite the fact that this compound has been used for at least three decades, important progress in the knowledge on maturational pharmacokinetics of morphine in neonates has been made only more recently. The predictability of morphine disposition has been documented in a stepwise approach. Based on pooling of pharmacokinetic observa-

tions on morphine disposition, model-based simulations suggested that in preterm neonates, a loading dose (μg/kg) and a maintenance dose (μg/kg$^{1.5}$/h), with an additional reduction (−50%) of this maintenance dose in neonates <10 days to result in a reasonable range of morphine and morphine metabolites [196]. These simulations were subsequently validated on its pharmacokinetic predictability in other datasets of morphine observations in neonates [197]. These pharmacokinetic models can subsequently been applied to validate or reject the above-suggested pharmacodynamic concentrations (120 and 300 ng/ml thresholds). Besides maturational weight (kg$^{1.5}$), specific disease characteristics like systemic hypothermia or the type of surgery may further affect morphine pharmacokinetics [198, 199].

Fentanyl is the first of a sequence of synthetic, fat-soluble opioids (sufentanil, alfentanil). It penetrates faster into the central nervous system because of the fat solubility, resulting in a faster effect as compared to morphine. Furthermore, fentanyl is a potent μ-opioid receptor agonist with a 70–125 times higher potency than that of morphine. Fentanyl is metabolized by N-dealkylation into non-active metabolites. It is considered to be short acting, but it has a prolonged elimination half-life in neonates when compared to older children and necessitates a similar level of monitoring in neonates. Tolerance is anticipated after about 3 days of exposure. However, Völler et al. recently described very rapid maturing fentanyl clearance in preterm neonates in the first week of life (threefold), so that tolerance should be discriminated from increased clearance capacity [200].

Muscular (thoracic) rigidity has been reported occasionally. Short-term analgesia can be achieved with the administration of 1–5 μg/kg, but is associated with respiratory depression. Sustained use can be started with the same loading dose, followed by 1–5 μg/kg/h [125, 201].

Recommendations on the use of opioids in neonates mainly depend on the indications, i.c. postoperative pain relief, procedural pain, or analgo-sedation during mechanical ventilation. The treatment of opioid related neonatal withdrawal/abstinence syndrome is outside the scope of this chapter. However, prevention and reduced opioid exposure is the obvious first step, and structured guidelines can assist on this. Implementation of guidelines on the use of opioids and sedatives were effective to reduce the utilization of these drugs and its variability [202]. This reduction in exposure was reflected in the number of patients (63–33%) and the cumulative dose (morphine −68%; midazolam −37%). Interestingly, this intervention also resulted in a significant reduction in the number of cases (−75%) requiring methadone treatment for iatrogenic opioid withdrawal [202].

In the setting of postoperative analgesia following "major" surgery, these compounds are recommended, as monotherapy or as part of multimodal analgesia. There is even evidence from a randomized controlled trial supporting the benefits of opioids on neonatal outcome [1]. Continuous infusions following a loading dose is most commonly applied for reasons of uniformity, safety, and simplicity although similar outcome has been documented when continuous administration of morphine was compared to intermittent administration [203]. It has been documented that acetaminophen (paracetamol) does result in a clinically relevant reduction in morphine consumption when integrated in multimodal analgesia [204]. Because of its shorter elimination half-life, continuous administration after a loading dose is even more common practice for fentanyl. This practice, i.c. intermittent bolus versus continuous fentanyl in preterm neonates, has been evaluated on its effectiveness in mechanical ventilated newborns [205].

In contrast, the evidence on the effective use of opioids for procedural analgesia is much more limited. Morphine administration does not blunt the pain scores related to endotracheal suctioning in ventilated newborns [206], and neither improves the pain response during heel lancing or blood sampling in neonates when compared to other interventions like oral sucrose [207].

This is at least in part due to the fact that morphine acts in the central nervous system. Consequently, there is a relevant lag time between the administration and the analgo-sedative effects. The same concept should be considered when morphine is administered to facilitate endotracheal intubation. In randomized controlled trials, morphine seems to perform worse if compared with remifentanil, fentanyl, or propofol [129, 156, 159]. Based on the clinical pharmacology of opioids, "fast-acting" opioids such as fentanyl or remifentanil are more appropriate. The same limited evidence holds true for analgo-sedation during mechanical ventilation.

Routine use of morphine cannot be recommended for ventilated (pre)term neonates because no obvious beneficial short-term outcome effects have been documented in meta-analytic exercises [207]. The reported short-term side effects associated with opioid exposure in preterm neonates include hypoventilation and apnea, low blood pressure, intestinal hypoperistalsis, and bladder dysfunction. Hypoventilation and apnea resulted in prolonged duration [7 (4–20) days in morphine exposed compared to 6 (3–19) in the placebo group, + 1 day of ventilation] [208]. Along the same line, Hartley et al. recently reported that morphine (single oral, 100 μg/kg dose) in non-ventilated preterm infants to facilitate screening for retinopathy of prematurity (ROP) and to blunt the pain response resulted in a high incidence (8/15 versus 3/15, relative risk 2.7, number needed to harm = 3) of newly occurring apneic events or an increase in the number of such events in morphine-exposed cases [209].

Moreover, studies suggest that preemptive morphine in ventilated preterm infants is associated with suboptimal neurodevelopmental outcome variables at the age of 5 and 8 years, respectively [210, 211]. The same advice can be pro-

vided for fentanyl. Based on a published study on the use of fentanyl in ventilated preterm neonates, there seems to be no place for *routine* continuous fentanyl infusion in ventilated preterm neonates. This is because of the absence of continued pain score reduction and increased side effects of continuous infusion compared with the bolus administration of fentanyl. Moreover, the use of boluses of fentanyl before invasive procedures or on the basis of pain scores has demonstrated the same efficacy and an improved safety profile compared with the continuous infusion of fentanyl [212]. This conclusion can be made based on a multicenter, double-blind, randomized controlled trial, mechanically ventilated newborns ($\leq 32^{+6}$ weeks gestational age), randomized to fentanyl ($n = 64$, continuous infusion of fentanyl plus open-label boluses of fentanyl), or placebo ($n = 67$, continuous infusion of placebo plus open-label boluses of fentanyl). The primary endpoint was analgesic efficacy, as evaluated by the EDIN and PIPP scales [205]. Interestingly, the need for open-label boluses of fentanyl was similar, and EDIN scores were comparable between both groups, while the median PIPP score was clinically and statistically higher in the placebo group compared with the fentanyl group on day 1 up to day 3 of treatment. When considering the side effects, mechanical ventilation at age 1 week was still required in 27 of 64 infants in the fentanyl group (42.2%), compared with 17 of 67 infants in the placebo group (25.4%) ($P = .042$). The first cycle of mechanical ventilation was longer and the first meconium passage occurred later in the fentanyl group ($P = .019$ and .027, respectively). Based on the body of evidence collected, fentanyl does reduce acute pain, but does not reduce prolonged pain with an additional cost of an increase in duration of ventilation or paralytic ileus [205].

Take-Home Messages

- Data on the pharmacokinetics of morphine and fentanyl have been reported, resulting in dosing guidelines to result in predictable exposure [196, 197, 200].
- There is strong evidence in support of the use of opioids in postoperative analgesia [1], but side effects include cardiorespiratory depression, bladder and intestinal paralysis, hypotension, and tolerance.
- Völler et al. described very rapid maturing fentanyl clearance in preterm neonates in the very first days or week of life (threefold), so that tolerance should be discriminated from increased clearance capacity [200].
- For procedural pain relief during major interventions (e.g., endotracheal intubation), opioids are somewhat effective with a shorter effect time for fat-soluble synthetic opioids [129, 156, 159].
- In contrast, there is no evidence supporting the routine use of opioids in ventilated newborns. It seems that opioids should be solely used to reduce acute and prolonged pain, but not to reduce prolonged pain during ventilation because of an increased duration of ventilation and an increase in paralytic ileus. Moreover, follow-up data suggest a link between the extent of opioid exposure and impaired neurological outcome.

Benzodiazepines

Benzodiazepines have their pharmacologic interaction at the level of the gamma-aminobutyric acid (GABA) receptor in the central nervous system. This interaction results in sedation with associated hypnosis, anxiolysis, muscle relaxation, and anticonvulsant activity, but does not relieve pain. Importantly, it has been documented that the GABA receptor switches from an excitatory to an inhibitory mode during early development, equal to preterm age. This may explain age-related differences in pharmacodynamic side effects, like agitation or muscular twitching. The most commonly used benzodiazepine is midazolam, with only very limited information on lorazepam or diazepam in neonates [212].

Midazolam's bioavailability is about 35% when given as oral syrup and 50% when absorbed directly through buccal or nasal mucosa. Midazolam undergoes extensive metabolic clearance, including hydroxylation to 1-OH-midazolam (cytochrome P450 3A), that also has some sedative effects and glucuronidation. Since these processes display maturation, clearance is reduced with an elimination half-life of 12 h in the neonate, compared to 2 h in the adult. Anderson and Larsson [213] described a maturational model of midazolam clearance and extrapolated that a steady-state infusion rate of 0.014 mg/kg/h is needed to attain a sedation target concentration similar to findings in adults. However, this dosing suggestion has not been validated. Recently, a new dosing advice for midazolam for sedation on intensive care units has been included in the label (0.03 mg/(kg/h) for preterm neonates <32 weeks and 0.06 mg/kg/h for neonates >32 weeks). However, simulations of this newly registered dosing show considerable differences in steady-state concentrations within preterm neonates [214].

Because major changes in phenotypic cytochrome P450 (CYP)3A activity can be anticipated in the first few months of life, the maturation of in vivo CYP3A-mediated clearance of midazolam from preterm neonates of 26 weeks gestational age (GA) to adults has more recently been evaluated by Ince et al. [215]. This exercise was based on pooling of pharmacokinetic data after intravenous administration of midazolam from six previously reported studies, including premature neonates. Across the entire lifespan from premature neonates to adults, bodyweight was a significant covariate for midazolam clearance. The effect of bodyweight was best described by use of an allometric equation with an exponent changing with bodyweight in an exponential manner from 0.84 for preterm neonates (0.77 kg) to 0.44 for adults (89 kg).

These findings confirm that indeed the most rapid maturation occurs during the youngest age range. Consequently, dosing should be lower in neonates, and accumulation is more likely to occur in early life [215]. Besides maturational covariates, disease characteristics (like critical illness, inflammation) affect midazolam clearance (up to −90% lower) in neonates and infants [216].

While midazolam is often used for premedication in children (oral, 0.5 mg/kg), a loading-dose approach (intravenous, 0.05–0.1 mg/kg) in preterm neonates commonly results in hypoventilation, hypotension, and reduction in cerebral blood flow. Some units give 0.06 mg/kg/h for sedation in ventilated neonates, with a dose reduction after 24 h to avoid accumulation. However, this approach is now increasingly questioned, because there is reluctance to use benzodiazepines in preterm neonates following the NOPAIN study. The NOPAIN multicenter study aimed to assess the feasibility to test the effect of analgesia or sedation (morphine versus midazolam versus placebo) on mortality and neurologic morbidity in a cohort of 67 preterm (24–32 weeks) neonates [217]. This pilot study suggested a statistically significant higher incidence of adverse neurological events with the use of midazolam (death, grade III or IV IVH, PVL). Based on the latest meta-analysis, data are still insufficient to promote the use of intravenous midazolam infusion as sedative for neonates during intensive care, while the same meta-analysis raised concerns about the safety (incidence of adverse neurological events) of midazolam in neonates [218].

Besides monotherapy for sedation during ventilation, there are also reports on the combined administration of midazolam with an opioid (morphine, fentanyl, or remifentanil) to achieve a more balanced analgo-sedation during ventilation. In a double-blind, randomized controlled trial in mechanically ventilated newborns and young infants (<60 days), a low dose of midazolam (0.05 mg/kg/h) was combined with remifentanil (3 μg/kg/h) or fentanyl (1 μg/kg/h). Both dosing schedules resulted in comparable efficacy, good hemodynamic stability, and a similar incidence of adverse events. Interestingly, the median extubation time after interruption of the sedation was significantly shorter in the remifentanil when compared to fentanyl (median duration 80 (IQR 15–165) compared to 782 (250–1875) minutes) [219]. In conclusion and based on the currently available evidence, the *routine* use of midazolam to facilitate ventilation in (pre)term neonates cannot be recommended, while midazolam is often used as additional treatment when analgesia is considered insufficient or as a means to decrease exposure to analgesics. Similar to monotherapy, this strategy is associated with hypotension, hypoventilation, and hypoxemia [220]. To further reflect this practice, midazolam was given to 576 (9%) of 6680 neonates, but to 536 (25%) of the intubated neonates in the EUROPAIN study [23].

Besides ventilation, there are also some reports on the use of benzodiazepines to facilitate endotracheal intubation. In a small (n = 20) randomized study in preterm neonates, the number of attempts and overall intubation conditions was not significantly different when midazolam was compared to propofol [131]. Another randomized, placebo-controlled double-blind trial in preterm neonates was stopped after 16 intubations because preterm neonates exposed to midazolam and atropine had more desaturations and required more frequently cardiopulmonary resuscitation [221]. In a randomized controlled trial in 60 neonates necessitating neonatal intubation in the delivery room, nasal midazolam (0.2 mg/kg) versus nasal ketamine (2 mg/kg) resulted in similar hemodynamic and respiratory effects, but nasal midazolam was more effective as sedative (higher success rate 89 versus 58%; shorter time until intubation, 10 versus 16 minutes) to facilitate intubation [150]. Finally, Pereira e Silva et al. reported in a double-blind randomized controlled trial in 20 preterm (28–34 weeks) neonates on intubation conditions following morphine (150 μg/kg) or remifentanil (1 μg/kg), both combined with midazolam (0.2 mg/kg). Overall intubation conditions were better in the remifentanil group [159].

Midazolam causes hypotension in both preterm and term neonates, decreases cardiac output, and decreases cerebral blood flow velocity in preterm neonates. Consequently, it seems that midazolam use for endotracheal intubation is not the best choice and should be restricted to (near)term neonates [222]. To further illustrate this, in a survey on the use of premedication for intubation in tertiary neonatal units in the United Kingdom, only a very limited number of units (6%) used midazolam (median dose 0.1 mg/kg) to facilitate endotracheal intubation. Similar, the American Academy of Pediatrics does not support the use of midazolam in preterm neonates, while it can be considered for use in term neonates and infants as part of the premedication sequence for elective intubation [222].

Finally, prolonged and cumulative doses of benzodiazepines have been associated with tolerance, physical dependency, and withdrawal syndrome, also in neonates. Similar to approaches in children or adults, the feasibility of sedation and analgesia interruption following cannulation in neonates on extracorporeal membrane oxygenation (ECMO) has been described in a prospective observational study in 20 neonates on ECMO [223].

Take-Home Messages

- Midazolam clearance is much lower in neonates. Consequently, population-specific dosing is required, and accumulation is more likely in neonates [213–215].
- A new dosing advice for midazolam for sedation has been included in the label (0.03 mg/kg/h] <32 weeks and 0.06 mg/kg/h >32 weeks). However, simulations of

this newly registered dosing show considerable differences in steady-state concentrations within preterm neonates [214].

- The use of midazolam quite commonly results in side effects, including hypoventilation, hypotension, and cerebral hypoperfusion. Midazolam has been associated with poorer neurological outcome in former preterm neonates [217, 218, 221].
- Routine use of benzodiazepines for sedation is not indicated in neonates. Prescription needs to be individualized and is most commonly part of a multimodal analgo-sedative strategy [212, 218].

Dexmedetomidine

Ideal analgo-sedation should be rapid in its onset of action, be predictable in its duration and depth of action, not depending on active metabolites (effects or side effects), and still result in rapid dissipation of effects on discontinuation of the agent, be non-addictive (physical dependence or withdrawal on discontinuation), without drug tolerance, and without adverse effects on cardiopulmonary function [16]. Preferably, this should be combined with a wide therapeutic index, absence of drug interactions, and incompatibilities with other drugs and without influence of underlying comorbidities, like renal or hepatic disease. We are unaware of such an ideal compound for neonates, but dexmedetomidine may become a potential useful asset to attain these objectives in neonates [16].

Dexmedetomidine is a potent lipophilic α2-adrenoreceptor agonist with a α2/α1 activity ratio of 1620/1. Its mechanism of action is thought to result from activation of G proteins by central postsynaptic α2-adrenoreceptors, increasing conductance through potassium ion channels, leading to inhibition of norepinephrine release. Through sympatholysis, dexmedetomidine exerts its sedative, analgesic, opioid-sparing, and anxiolytic properties, as well as its side effects like hypotension or bradycardia. Of interest are also the cardioprotective properties through blunting stress-response effects after surgery, positive effects on facilitating extubation and (postoperative) delirium, and the claimed neuroprotective effects [224]. Currently, dexmedetomidine is approved for short-term analgo-sedation (<24 h) in mechanically ventilated critical care adult patients and sedation of non-intubated adult patients prior to and/or during surgical and other procedures. Trials are underway to investigate its pharmacokinetics, clinical efficacy, and safety in long-term use, but there is already clinical experience with long-term administration of this drug in the adult ICU [225, 226].

In contrast, clinical experience with dexmedetomidine in the pediatric population is still rather limited in neonates. Dexmedetomidine has some reported advantages over standard sedation regimens with regard to adverse drug reactions, does not affect respiratory drive, and can facilitate a shorter duration of mechanical ventilation compared to fentanyl-treated controls. Dexmedetomidine seems to have minimal impact on gastric motility: neonates treated with dexmedetomidine require a shorter time to reach full enteral feeds compared to neonates treated with fentanyl. Finally, in vitro and animal experimental studies suggest neuroprotective effects [16, 224–226].

Unfortunately, dexmedetomidine also has the potential for significant adverse drug reactions. The most concerning is hypotension, which is common with bolus doses of dexmedetomidine in both adult and pediatric patients. The incidence and degree of hypotension after bolus dosing appears to be similar to that typical of fentanyl and midazolam. Avoidance of bolus doses or rapid titration of dexmedetomidine attenuates this effect, at least in adults. Because of the pathophysiology of hypotension (related to central α2-adrenoreceptor agonism), the subsequent treatment is more difficult and the duration prolonged.

Currently, the experience with dexmedetomidine is limited in neonates, but includes, e.g., neonates on ECMO [227] or its use as midazolam-sparing drug for medical imaging in former preterm neonates at term equivalent age [228]. Its pharmacokinetics have only more recently been described in newborns, but include preterm neonates and term neonates after open heart surgery [225, 229, 230]. The hemodynamics following dexmedetomidine (loading dose 1 μg/kg within 10 minutes, followed by 0.5–0.8 μg/kg/h) exposure during anesthesia for abdominal surgery in 16 neonates have been reported. As adjacent to sevoflurane anesthesia, hemodynamic stability (heart rate, diastolic and systolic blood pressure) was observed [226]. Shukry et al. reported on the use of dexmedetomidine to facilitate direct laryngoscopy and bronchoscopy in four infants, including one newborn (2 weeks to 11 months) [230]. The total dexmedetomidine dose used was 2–5 μg/kg, and one patient (the newborn) needed one additional dose of propofol (3.7 mg/kg). Heart rate and mean arterial blood pressure remained stable throughout the procedure (7–38 minutes)[229]. Finally, there is a case report in a single newborn co-treated with dexmedetomidine (0.09–0.53 μg/kg/h) in combination with midazolam (0.15 mg/kg/h) and fentanyl (0.8 μg/kg/h) to facilitate analgo-sedation in a setting of airway compromise related to a congenital mediastinal neuroblastoma. Plasma dexmedetomidine concentrations were 0.25–0.65 ng/ml, and sedation (COMFORT score) was adequate [231]. In a retrospective analysis on neonates either or not co-exposed to dexmedetomidine after surgery, the addition of dexmedetomidine to opioid infusions resulted in a significant decrease in opioid (−37%, 1155 versus 1841 μg/kg) needs, but was associated with more bradycardia events (twofold increase, 12.8 versus 5.1%) in dexmedetomidine-exposed cases [232]. Along the same line

but in an randomized controlled trial study, neonates and infants (<3 months) with dexmedetomidine + caudal block ($n = 51$) had significantly lower heart rates, higher mean arterial blood pressure when compared to inhalational (nitrous oxide, sevoflurane) anesthesia, and intubation + caudal block ($n = 48$), but needed less frequent intensive care admission (3.9 versus 12.5%), and this technique avoided intubation in 49/51 dexmedetomidine cases [233].

Further studies to define the incidence and clinical impact of this effect in preterm neonates are necessary. Such prospective studies of dexmedetomidine in preterm neonates must include continuous assessment of blood pressure and heart rate as well as utilize available technologies to assess perfusion. As a final warning, we refer to the case report on seizures, likely induced by dexmedetomidine in one neonate [234]. This can be explained by the dexmedetomidine-related reduction in the anticonvulsant activity of the locus ceruleus.

Take-Home Messages

- Based on its pharmacokinetics and dynamics, dexmedetomidine holds the promise to become a useful compound for analgo-sedation in neonates [225, 226, 228–233].
- At present, data are accumulating, and we highly recommend colleagues to report on their experience with this drug in order to increase the available information in order to get a valid impression on risk/benefit profile in neonates.

Inhalational Agents

The number of studies and the clinical application of inhalational agents for procedural analgo-sedation in neonates and young infants are – to the best of our knowledge – limited to equimolar nitrous oxide (N_2O)/oxygen mixture (retinopathy of prematurity screening, intramuscular palivizumab administration) and single unit experience with sevoflurane (central catheter placement, endotracheal intubation). Even more relevant, we could not retrieve new data or reports on these practices in the last 5 years.

In line with the available knowledge on the age-related analgesic effects of equimolar nitrous oxide (N_2O) and oxygen [235], a randomized controlled trial documented that this inhalational strategy did not result in any additional pain relief during eye screening examinations in preterm neonates [236]. The mean PIPP score at speculum insertion in the control group (8.4, 95% CI 7.6–9.3) was comparable with the nitrous oxide exposed group (8.5, 95% CI 7.3–9.8). There were no significant differences in oxygen saturation or heart rate between both groups. Inhalation was tolerated without any measured side effects [236]. Using an at random study design, infants receiving palivizumab administration received nitrous oxide (50/50 mixture), EMLA application, or both. Pain assessment was based on the Modified Pain Behavior Scale (MPBS). Although there was a significant lower MBPS during nitrous oxide administration – most pronounced when combined with EMLA – the mean overall MBPS rating during immunization and recovery period were still 8 and 7, respectively [237]. These mean values are similar to those reported in another cohort of former preterm neonates during palivizumab immunization in which MPBS was assessed without any specific intervention [238].

The Montpellier unit reported the use of sevoflurane for procedural analgo-sedation in neonates [239–241]. Using a stepwise increase until loss of consciousness and motor response in 33 consecutive cases to facilitate central venous catheter placement, heart rate remained stable, but mean arterial blood pressure dropped, while none of the patients required intubation [239]. The ease of the procedure was scored as "average" 13 times and "excellent" 20 times [239]. This report followed an earlier reported randomized controlled trial in 55 neonates, aimed at comparing efficacy and safety of sevoflurane with glucose and non-nutritive sucking (GNNS) analgo-sedation in reducing the duration of the procedure and in preventing pain-related effects during PICC placement [240]. Sevoflurane exposure resulted in greater immobility and fewer episodes of hypertension and tachy- or bradycardia. Occurrences of hypotension were not different, while the glucose group showed more desaturation during the 4 h after the intervention. The same group reported on the use of sevoflurane for endotracheal intubation [241]. Thirty-three neonates were randomized to sevoflurane (inspired concentrations 2–5%) or no medication (pre-oxygenation with 100% oxygen) before endotracheal intubation. No major differences in the incidence of adverse events were noted in the study group compared with controls (hypotension (37.5 versus 37.5%), desaturations (37.5 versus 44.5%), while hypertension (25 versus 56.3%) and bradycardic events (8.3 versus 44.4%) were more frequently observed in the control group. Moreover, intubation was easier in the sevoflurane group, with specific emphasis on the absence of movements (95.5–28%), optimal glottis visualization (73–33%), and failure rate (25–39%). Because of the use of a "placebo-controlled" study design, it is not really possible to compare these outcome data with more commonly applied pharmacological strategies to facilitate endotracheal intubation [241].

Before we consider the use of inhalational agents for analgo-sedation in neonates, we should be aware of the maturational pharmacodynamic differences and of the logistics involved. To illustrate the age-dependent pharmacodynamics, we refer to the available data on halothane. Lerman et al. found that the minimum alveolar concentration (MAC) of halothane in neonates (0.87%) was significantly lower than that in infants (1.20%), while the MAC in infants were significantly higher when compared to older children [242].

With induction of anesthesia, the systolic blood pressure decreased 23% in neonates and 34% in infants. Similarly, the heart rate decreased 12% in neonates and 22% in infants, and hypotension was not significantly different (33–44%). The authors concluded that the MAC of halothane for neonates is 25% less as compared to infants and significantly less than was thought previously without any difference in the incidence of cardiovascular side effects. Secondly, the logistics needed mainly relate to the avoidance of air pollution, commonly in part achieved by the use of closed loop circuits. Consequently, this means that specific ventilation equipment is needed.

Take-Home Messages

- There are limited data on the use of inhalational agents in neonates. Even more relevant, it seems that there are not really new data or reports on these practices in the last 5 years.
- Because the logistics needed, its use will very likely remain limited.

Acetaminophen (Paracetamol)

Clinical pharmacology of acetaminophen in neonates

Acetaminophen, N-acetyl-p-aminophenol (paracetamol), is a readily available, over the counter (OTC) antipyretic and analgesic agent. It is the most often prescribed drug for treatment of mild to moderate pain or fever, also in infants and neonates, and can be administered by oral, rectal, but also intravenous route [243]. Data on prescription practices in the NICU setting are still fragmented and anecdotic for acetaminophen, with an overall pattern suggesting that acetaminophen is the "rising star" in NICU pain management. This is reflected in the Pediatrix database and the NEOPAIN study [23, 191, 192]. While absent in the top 30 in the first (1997–2004) cohort, acetaminophen appeared on position 16 with 43/1000 in the more recent (2005–2010) cohort analysis [191, 192]. In the EUROPAIN study, acetaminophen prescription (14%) was more common than sedative/hypnotics (12%), but still lower compared to opioids (26%) [23].

Acetaminophen is widely used in the management of pain, but has – if any – only very limited peripheral anti-inflammatory effects [244, 245]. While the acetaminophen peak concentration occurs approximately 60 minutes after oral dosing, absorption after rectal administration is variable and prolonged. Intriguingly, the mechanisms of actions for acetaminophen are still only partially unveiled. There is concentration-dependent inhibition of the prostaglandin H2 synthetase (PGHS) enzyme. This PGHS complex has two sites: the cyclooxygenase (COX) and the peroxidase (POX) site [244–247]. Acetaminophen hereby acts by reducing co-substrate in such a way that less prostaglandin G_2 can be converted to prostaglandin H_2 at the POX site of this PGHS enzyme. Acetaminophen-related POX inhibition is competitive since counteracted by prostaglandin G_2 itself or by lipid hydro-peroxides. This explains why the inhibition of prostaglandin synthesis is potent within the central nervous system (no lipid hydro-peroxides, since the main sources of these peroxides are leukocytes and platelets). Outside the central nervous system, acetaminophen has also non-selective inhibitory action on peripheral COXs. However, this inhibitory action only relates to physiological, low arachidonic acid concentrations, and this explains the difference with, e.g., ibuprofen, that has more robust anti-inflammatory peripheral effects in an inflammatory (high hydro-peroxides, high prostaglandins) setting [245]. Other mechanisms relate to the formation of an active metabolite (p-aminophenol) that interacts with cannabinoid receptors. Its analgesic effects are further mediated through activation of descending serotonergic pathways, substance P-mediated processes or interaction with the N-methyl D-aspartate (NMDA)-receptor and effects by nitrous oxide as spinal neurotransmitter [244–247].

In the therapeutic concentration (median claimed to be 10 mg/l) range, acetaminophen is metabolized by the liver to acetaminophen-glucuronide (47–62%) and acetaminophen-sulfate (25–36%) as main metabolites and subsequently eliminated by renal route. Only 1–4% is excreted unchanged in urine, and about 8–10% of acetaminophen is oxidized to 3-hydroxy-acetaminophen and the (hepatic) toxic metabolite N-acetyl-p-benzoquinone-imine (NAPQI) [243]. Data on the clinical pharmacology of acetaminophen, including pharmacokinetics and tolerance (hepatic, hemodynamics) in neonates following enteral or intravenous route, have been published. Clearance mainly relates to weight, age, and – to a limited extent – hyperbilirubinemia [248–252]. Besides data on overall clearance, detailed information on the various routes of elimination (glucuronidation, sulfation, oxidation, renal) and their maturational trends have been reported and subsequently validated [248, 249].

Hepatic tolerance and hemodynamic tolerance have been documented during repeated administration [246]. Consequently, acetaminophen is perceived to have a good efficacy-to-safety ratio as analgesic in a wide range of patient populations. However, since acetaminophen is one of the most commonly used drugs to treat pain or fever, knowledge on the covariates of acetaminophen disposition remains crucial to avoid toxicity through unanticipated variability. In addition to oral and rectal formulations, several intravenous formulations became available more recently. Such a formulation enables the administration of acetaminophen when the enteral route cannot (yet) be used and should improve the predictability by the reduction in variability related to absorption [250, 251].

Efficacy

Based on the available evidence, acetaminophen has opioid-sparing effects for major pain syndromes, is effective to treat minor to moderate pain syndromes, but fails for effective procedural pain management in neonates. The concept of multimodal "opioid-sparing" analgesia has initially been introduced in the NICU without robust evidence on this practice. Only more recently (2013), Ceelie et al. documented an clinical significant (−66%) morphine (maintenance dose)-sparing effect in neonates co-treated with IV acetaminophen compared to placebo following major, noncardiac surgery [204]. Along the same line, an opioid-sparing effect (cumulative dose −54%; cumulative number boluses −59%) has also been observed in a retrospective analysis on opioid consumption in preterm neonates (<32 weeks) before and after introduction of acetaminophen (iv) in the clinical protocol of a single NICU [253].

In contrast, the data on acetaminophen analgesia during painful procedures consistently provide evidence for an overall poor analgesic effect when used for procedural pain relief. The available information strongly suggests that acetaminophen fails to reduce acute procedural (skin-breaking procedures like heel lancing or PICC placement, ROP screening) pain [254]. Compared to placebo, there was no benefit in cases exposed to acetaminophen, while the effect of acetaminophen was inferior when compared to non-pharmacological interventions (like sucrose or dextrose). Similar, Roofthooft et al. also concluded that intravenous acetaminophen (10, 15 or 20 mg/kg) was not effective (PIPP score, COMFORT-neo) as an analgesic during PICC placement in 60 preterm (<32 weeks) neonates, irrespective of the dose administered [255]. This is line with similar findings on the absence of an analgesic effect of high doses (40 mg/kg oral) of acetaminophen on pain, fear, or distress as reported by children undergoing needle insertion into a subcutaneously implanted intravenous port [256]. In this way, results in neonates are similar to those observed in children.

Acetaminophen (15 mg/kg, oral) was neither found to ameliorate intraoperative nor immediate postoperative pain following circumcision, although it seems that it may provide some benefit after the immediate postoperative (>6 h) period [257]. The effects of acetaminophen (20 mg/kg, rectal) on neonates following vacuum extraction has been documented by Van Lingen et al. [258]. Based on a randomized, placebo-controlled study design in 122 neonates delivered by vacuum extraction, one dose of acetaminophen significantly improved their clinical condition (e.g., drinking behavior), but did not result in a significant change in objective pain scores, and there were no positive effects following repeated administration. Using a preemptive approach and a placebo-controlled study design in 123 term neonates following assisted vaginal delivery, infants born by assisted vaginal delivery had low pain scores in the immediate period after birth, irrespective of acetaminophen exposure. Intriguingly, acetaminophen (20–25 mg/kg, rectal) given to term newborns shortly after birth was associated with an aggravated subsequent stress response during heel lancing on day 2–3 of postnatal life [259].

Safety

The hepatic tolerance during repeated administration has been mentioned earlier. However, there are case reports on hepatic failure following acetaminophen exposure in neonates. Unfortunately, most of these cases can be explained by the well-known tenfold overdosing error (intravenous formulation, 10 mg/ml). Another population specific indication in preterm neonates is to be mentioned is the use of acetaminophen to induce closure of the patent ductus arteriosus as emerging practice [260, 261].

Long-term epidemiological association types of studies reported on safety concerns relate to neurobehavioral (attention deficit hyperactivity disorder, autism spectrum disorders, intelligence) outcome, atopy, or fertility (cryptorchidism). At present, these data are mainly driven by epidemiological observations following maternal intake and subsequent fetal exposure. The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) examined the available observations in 2015 and 2019, respectively, and concluded that the clinical relevance of these potential associations is still unknown, leading to the decision not to change their advices, while the leaflets (summary of product characteristics, SmPC) have been adapted in the specific section on fertility, lactation, and pregnancy [262].

Take-Home Messages

- Data on acetaminophen pharmacokinetics/dynamics have been published and suggest that the same effect compartment concentration (10 mg/l) of acetaminophen should be aimed for in neonates [248–252].
- This means that a loading dose should be considered (intravenous or oral 20 mg/kg, rectal 30–40 mg/kg), followed by maintenance (intravenous or oral 10 mg/kg, rectal 1–18 mg/kg) doses (in term neonates q6h, in preterm (<32 weeks) neonates q8h) [250].
- Data on safety suggest that acetaminophen has indeed a short-term good safety profile in neonates when administered for a limited time (48–72 h).
- There are emerging data on association studies between acetaminophen exposure and neurobehavioral (attention deficit hyperactivity disorder, autism spectrum disorders, intelligence) outcome, atopy, or fertility (cryptorchidism) [243, 262].

- It has been published that – similar to children and adults – (IV) acetaminophen has indeed opioid-sparing (−66%) effects in neonates after major noncardiac surgery [204].
- Acetaminophen is a very poor analgesic for procedural pain relief [254].

Neonatal Analgo-sedation: Balancing Between Scylla and Charybdis

Non-pharmacologic as well as pharmacologic treatment of pain became an indicator of quality of care in neonates following the pivotal report of Anand et al. in the late 1980s, demonstrating the ability of newborn infants to feel pain [1]. Ineffective treatment of pain in these vulnerable individuals was not only inhumane [18, 19], but likewise also resulted in worse health outcomes [2, 14]. In essence, these observations strongly suggest that early pain experience contributes to neurodevelopmental outcome, pain thresholds, pain- or stress-related behavior, and physiological responses in later life. Effective management of pain therefore remains an important indicator of the quality of care provided to neonates, not only from an ethical but also from a short- and long-term outcome perspective [2, 14, 18, 19]. However, further adaptations and patient tailoring is needed, because of both newly emerging data on neuro-apoptosis associated with exposure to analgo-sedatives as well as simultaneous changes in neonatal care itself [8–12, 16].

The ontogeny of the nervous system is based on a complex pattern of cell proliferation, migration, differentiation, and selective cell death by apoptosis. Functional development relates to a balance of excitatory and inhibitory signals. Due to maturational plasticity of the nociceptive systems throughout infancy, nociceptive input may cause population-specific lasting alterations in pain processing. Similarly, exposure of nociceptive and non-nociceptive nervous circuits to analgo-sedatives also modulates receptor signaling-related brain development. Experimental data from animals provide evidence that chronic morphine exposure in perinatal life results in reduced brain volume, decreased neuronal packing density, and less dendritic growth and branching. This is associated with learning and motor disabilities. In contrast, opioid receptor blockade through naloxone results in increased brain size and more pronounced dendritic arborization. Similar animal experimental data have been reported for other analgo-sedatives, including benzodiazepines, ketamine, inhalational anesthetics, propofol, and barbiturates or combinations of these analgo-sedatives [8–12]. Alterations are in part drug and dose dependent, and there is an age-related window of vulnerability for apoptosis on the one hand or dendritic changes on the other hand. The extrapolation of these observations in animals to the human (pre)term newborn is obviously hampered by several limitations. Some authors report on an association between major neonatal surgery (number of interventions, disease severity) and neurodevelopmental impairment. However, exposure to analgo-sedatives is only one of the factors associated with this negative outcome [12]. Furthermore, exposure to general anesthesia compared to awake-regional anesthesia in infancy (GAS study) to undergo inguinal hernia repair in infants (<60 weeks postmenstrual age) was not associated with any difference in neurodevelopmental outcome (IQ assessment) at the age of 5 years [15].

The shifts in neonatal care refers towards less invasive care, as reflected by introduction of minimal enteral feeding to shorten duration of parenteral nutrition, while duration of endotracheal ventilation was shortened through early nasal CPAP, INSURE, or LISA approach [16].

First, adequate pain management is not an isolated activity. It should be an integrated part of developmental care. Behavior in former preterm infants was associated with the level of both developmental care ["infant-centered care" (ICC) index, parents' involvement in the care of their infant, and developmental oriented care interventions] and pain management ["infant pain management" (IPM) index, approach to and procedures used for reducing infant pain]. A higher ICC was associated with higher scores for attention and regulation, less excitability, and low stress scores, while higher IPM scores were associated with higher attention, higher arousal, and lower lethargy. The association between both suggests that the combination of both practices (ICC and IPM) support better neurobehavioral stability [263]. In our opinion, non-pharmacological methods for analgesia are the link between pharmacological analgesia and developmental-oriented care interventions, with focus on how parents can contribute to this [66].

Second, the introduction of analgo-sedatives and techniques also resulted in new clinical syndromes like opioid induced tolerance, neonatal drug withdrawal syndrome, hyperalgesia, or complications like drug-related toxicities or toxicity due to locoregional techniques. Tenfold dosing errors with intravenous acetaminophen and propofol infusion syndromes have been reported. Caregivers should be aware of contemporary management of the abovementioned complications.

In the clinical setting, a structured approach is needed [50–52]. There is no doubt that all NICUs need to adapt a validated pain assessment tool and an algorithm outlining the

responses of health-care providers if abnormal pain scores are detected. Reaching consensus within the NICU care team on the interpretation of an abnormal pain score and developing an algorithm of care for each pain scenario is crucially important. The same algorithm should also provide pathways for infants who do not respond to the treatment or develop adverse events. Although pain assessment tools have their limitations, such a structured approach should start with the routine use of a validated pain-assessment score for a given age group and should be followed by a condition-specific pain management protocol with a limited number of compounds ("tool box") so that caregivers are aware of (side) effects of these compounds. Table 18.6 provides some dosing suggestions. The dosing suggestions are based on dosing regimens reported in the literature.

Table 18.6 Dosing suggestions for different analgo-sedatives as extracted from the literature. This in part also reflects the overall limited information on dosing in neonates

Topical/local anesthetics	EMLA: 0.5–1 g, one application daily
Propofol (Table 18.4)	*Intubation*: 1–3 mg/kg, intravenous bolus
	Continuous: manual dosing regimen has been suggested, but has not yet been validated [140].
Ketamine	Still limited data, commonly part of multimodal analgo-sedation
Remifentanil (Table 18.5)	*Intubation*: 1–3 μg/kg, commonly part of multimodal analgo-sedation
	Continuous: 0.1–2 μg/kg/min during procedure
Chloral hydrate	25–75 mg/kg/dose, orally or rectally.
Morphine	*Intermittent*: 50–200 μg/kg/dose, IV/IM/SQ, q4h
	Continuous: loading 50–100 μg/kg over 1 h, followed by 5–20 μg/kg/h.
Fentanyl	*Intermittent*: 0.5–4 μg/kg, iv slow push, as required (q2h–q4h)
	Continuous: 0.5–3 μg/kg/h.
Midazolam	*Intermittent*: 0.05–0.15 mg/kg over at least 5 minutes, (q2h–q4h)
	Continuous: 0.01–0.06 mg/kg, per hour.
Dexmedetomidine	*No firm dosing advice available, practices vary*
	Loading dose 1 μg/kg within 10 minutes, followed by 0.5–0.8 μg/kg/h
Acetaminophen	*Intravenous*: loading dose 20 mg/kg, maintenance 10 mg/kg/dose
	Oral: loading dose 20–25 mg/kg, maintenance 12–15 mg/kg/dose
	Rectal: loading dose 30 mg/kg, maintenance 12–18 mg/kg/dose.
	Maintenance intervals: q6h (term), q8h (32–36), q12h (<32 weeks)

These pain management protocols should also focus on the titration of analgesics, including a decision tree on when and how to increase and decrease exposure to analgesics. Until more advanced tools to assess pain become available, we have to apply a validated pain assessment tool in clinical practice and train the NICU health-care providers in using these tools in a standardized way to guarantee an acceptable inter-observer variation in assessing neonatal pain [50–52, 57].

A promising approach to facilitate more effective implementation of better practices to improve pain management of neonates has been described by Dunbar et al. [57]. Twelve NICUs in the Neonatal Intensive Care Quality Improvement Collaborative focused on improving neonatal pain management and sedation practices. Collaborative quality improvement techniques were used to facilitate local quality improvement in the management of pain in infants. In essence, these units developed and subsequently implemented evidence-based better practices for pain management and sedation in neonates. The group introduced changes through plan-do-study-act cycles and tracked performance measures throughout the process. Strategies for implementing potentially better practices varied between NICUs on the basis of local characteristics. Individual units identified their barriers to implementation, developed tools for improvement, and subsequently shared their experience with the collaborative. Using this approach of collaborative quality improvement techniques enhanced local quality improvement efforts and resulted in effective implementation of potentially better practices at participating NICUs [57]. As similar effort in Japan resulted in a similar outcome (improved use of pain assessment tools, interventions based on these assessments, and the subsequent effects of these interventions) [264]. Our intersubjective opinion on how to improve pain management in neonates has been summarized in Table 18.7.

Finally and obviously, further studies are needed. We suggest that this research agenda covers (i) the development and validation of more sophisticated pain assessment tools integrating neurobiological evaluation, (ii) the collection of long term outcome data after neonatal exposure to analgo-sedatives (pharmacovigilance), and (iii) the use of an appropriate study design for neonatal pain studies. We encourage clinicians, but also ethical committees and other stakeholders involved, to design dose-finding studies needed to improve adequate (i.e., effective, neither over- nor underexposure) administration of analgo-sedatives in neonates.

Table 18.7 An inter-subjective opinion: *how to improve pain management in neonates*

Prevention
Any effective pain relief program should be integrated in a more extensive program with focus on reduction of environmental stress and facilitation of neuromotor and cognitive development. Parental involvement is hereby crucial and pivotal
Reduce the frequency of avoidable painful procedures: that's an obvious one, but not so easy to implement (e.g., frequency of endotracheal suctioning, skin breaking procedures)
Use the most appropriate technique to avoid stress or pain, as has been illustrated for blood sampling, endotracheal suctioning, screening for retinopathy of prematurity, or retinal surgery
Assessment
Systematic evaluation of pain based on a validated pain scale is crucial. Delegate the responsibility not only to assess but also to act: delegate the treatment of pain and the titration of pharmacological treatment within predefined ranges and predefined decision trees to the bedside caregiver
Systematic assessment of pain instead of ad hoc registration results in an increased awareness to treat and prevent pain.
Treatment
Introduce unit-specific recommendations for individual procedures, interventions, or clinical diagnoses based on validated non-pharmacological and pharmacological interventions. Such protocols should also consider weaning strategies and assessment and treatment of withdrawal syndromes
Titrated administration of analgesics in order to protect long-term neurological outcome should focus not only on a step-up but also on a step-down strategy.
You better know what you prescribe: limit your pharmacological tools to some compounds and know their effects and side effects instead of introducing too many different compounds: experience matters. If you use newer drugs, please consider to collect prospective data on their efficacy and safety in neonates or contribute to clinical trials. Long-term safety and pharmacovigilance – with all its caveats when assessed in this population – matters

Case studies

Case 1

The mother of a 2-month-old infant worries about immunization-related pain. She mentioned that the older sister of this infant is afraid of any medical intervention, while the mother herself has needle phobia, even resulting in avoidance of medical care when needed. In fact, the mother asks you to write a certificate that her infant does not tolerate any vaccination and, consequently, should not receive any vaccination. During the discussion, the mother wants to know if there is existing evidence for effective interventions to alleviate immunization-related pain in young infants.

Issues

Procedural analgesia There is meta-analytical evidence on the effectiveness and tolerability of different pharmacological, physical, procedural technique-related, psychological interventions and combination of these individual interventions to alleviate immunization-related pain. Pharmacological interventions relate to topical local anesthetics, sweet-tasting (sucrose 30%, glucose 24%) solutions, and combined analgesic interventions, including breastfeeding, were associated with reduced pain during childhood immunizations and should be recommended for use in clinical practice. Physical interventions: pain during immunization can be decreased by injecting the least painful formulation of a vaccine, having the child sit up or holding an infant, stroking the skin or applying pressure close to the injection site before and during injection. Other effective interventions relate to injecting the least painful vaccine first when two vaccines are being administered sequentially during a single office visit and performing a rapid intramuscular injection without aspiration. Psychological interventions related to parental breathing exercises, child-directed distraction, nurse-led distraction, and combined cognitive-behavioral interventions to reduce the pain and distress associated with routine childhood immunizations. Parents and health-care professionals should be advised to incorporate these psychological interventions to reduce the pain and distress experienced by children during immunization. Using a robust testing process, the HELPinKIDS program developed a parent-directed educational pamphlet and video about management of vaccination pain based on these abovementioned approaches (*further reading*: www.sickkids.ca/Learning/Stories/Knowledge-Translation/anna-taddio.html).

Relevance of post-vaccination treatment of fever/pain The administration of acetaminophen before immunization does not reduce the procedural-related pain. While prophylactic acetaminophen administration has been associated with a modest reduction in fuzziness or fever in the hours after immunization, this has also been linked with a reduction in the immunological response (antibodies). Consequently, systematic prophylactic administration of acetaminophen seems obsolete.

Case 2

Neonatal respiratory care has shifted from prolonged mechanical ventilation following endotracheal intubation towards nasal respiratory support through nasal CPAP or high flow nasal cannula. However, there is overwhelming evidence in support of early curative or even perhaps prophylactic endotracheal administration of surfactant in extreme low birth weight infants. This presents clinicians with a dilemma: endotracheal intubation warrants effective analgo-sedation in order to avoid mechanical trauma and pain, while prolonged analgo-sedation will result in failure to extubate shortly following surfactant administration. There is a

growing body of evidence in support of such an INSURE approach. Still, clinicians still struggle with the difficult balance between avoiding mechanical ventilation and preventing pain or stress in preterm neonates.

Potential Options, To Consider

Non-pharmacological interventions Some groups consider to adapt the applied technique to prevent stress or pain. Besides experimental research related to aerosol and inhalational disposition, this mainly translates into a less invasive technique by using a nasogastric tube to access the trachea instead of the commonly used endotracheal tubes. There is evidence on the feasibility of early administration of surfactant via a thin catheter during spontaneous breathing. This strategy further reduces the need for mechanical ventilation as compared to the INSURE approach, but still needs prospective confirmatory studies.

Pharmacological interventions Successful analgo-sedation for an INSURE approach does not only relates to effective analgo-sedation during endotracheal intubation but also relates to effective extubation shortly afterwards. As a consequence, the usual combination strategies (e.g., morphine/atropine/suxamethonium) fail to a large extent because it does take time until morphine is sufficiently effective, and it does take time until morphine is sufficiently cleared from the central nervous system. Alternative strategies based on propofol have been reported as effective to facilitate effective analgo-sedation for the INSURE approach (Table 18.4). Based on the available reported dose-seeking studies and clinical cohort data, we suggest the following dose range (propofol 0.5–2 mg/kg, to be titrated to effect). In contrast, remifentanil seems to be associated with limited efficacy and relevant side effects like chest rigidity (Table 18.5).

Case 3

As part of a quality improvement program, you are asked to advice on how to manage procedural-related pain associated with the routine blood sampling for metabolic screening in newborns.

In the approach to be taken, we refer to Fig. 18.1 of this chapter, with emphasis on prevention, non-pharmacological and pharmacological interventions.

Prevention Venous puncture is more effective (less punctures, shorter) compared to heel lancing.

Non-pharmacological interventions Facilitated tucking in combination with non-nutritive sucking (Table 18.2), sucrose 24%, or glucose 30% with pacifier or breast feeding is effective.

Pharmacological interventions In contrast, morphine (Carbajal Pediatrics 2005), paracetamol [105] or local anesthetics (Table 18.3) are not effective and fail to reduce pain during this procedure.

Case 4

Circumcision in the newborn is still in high demand in many countries across the globe including the United States. With the rapidly emerging information about the potential risks of exposure to inhalational or systemic anesthetic medications, especially the increased risk of neuro-apoptosis, there is more and more resistance in the medical community to perform circumcision under general anesthesia or even under conscious sedation with, for instance, the use of propofol. This clearly present clinicians with a dilemma when parents want their (pre)term neonate to be circumcised. So, what are the potential options to consider if indeed parents want their newborn infant to be circumcised during their stay in the neonatal intensive care unit.

Scenario Parents of a clinically stable preterm neonate (gestational age, 24 weeks; postnatal age, 4 weeks; current weight 650 g) want their newborn infant to be circumcised and are very persistent in this request.

Potential options to consider are:

1. Try to convince the parents that circumcision in such a small male infant is not only technically challenging taking into consideration the size of the penis of an infant with a total weight of 650 g but, even more, that adequate prevention of pain during and after the procedure might worsen the long-term outcome of their infant. Your advise is to postpone the circumcision to a later stage in infancy.
2. Perform the circumcision after explaining the parents all the aforementioned risks under local anesthesia. Use a penile block (technically very challenging in this size patient) or cream containing lidocaine/prilocaine. With the latter option, it is prudent to check methemoglobin concentrations in the infant because of the developmentally low expression of methemoglobin reductase. In a relatively small group of preterm infants with a gestational age of less than 32 weeks, no major issues have been detected. Therefore, based on the fact that this infant is already 4 weeks old, the risk is relatively low.
3. Perform the circumcision after explaining the parents all the aforementioned risks under general anesthesia. In general, most institutions will require that the infant be a minimum of 60 weeks postmenstrual age in order to undergo an anesthetic for this elective procedure.

AU9 AU10

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