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Pain and distress management in palliative neonatal care

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ABSTRACT

Palliative care concentrates on preventing and relieving suffering by reducing the severity of disease symptoms. Consistent treatment of pain and distress must therefore be an integral component of every palliative care concept. In this review non-pharmacological and pharmacological measures for pain and distress management in the context of palliative neonatal care are summarised. Furthermore, recommendations are given focusing on two special palliative neonatal care settings: compassionate extubation and withdrawing artificial nutrition and hydration.

1. Introduction

Palliative neonatal care is person- and family-centred care provided for a neonate with a progressive, advanced, life-limiting disease for whom the primary goal is to optimise the quality of life [1]. The evidence base in pediatric palliative care is not robust and there is a paucity of evidence specific to neonates. Accordingly, for this review on pain and distress management in palliative neonatal care we aimed to integrate published scientific research evidence with clinical expertise.

Among many other factors such as hunger and thirst, over-stimulation through noise and light, or separation from parents, pain is the leading cause of physical and psychological distress reducing the quality of life of neonates receiving palliative care. Bringing pain and distress in neonates with life-limiting conditions under control therefore has to be a core skill of every multiprofessional team caring for these vulnerable patients.

Knowledge about the physiology, diagnostics and therapy of neonatal pain has grown steadily. National and international recommendations on pain management for newborns who need intensive care have been published [2]. However, all these recommendations are based on research data of newborns under non-palliative care. As long as there are no specific studies for symptom assessment and treatment in newborns in palliative care situations, pain and symptom control must follow the basic principles that have been published for all neonates cared for in neonatal intensive care units. The following aspects of pain and distress management should be incorporated in any palliative neonatal care concept:

- The basis of symptom control in neonatal care is a form of care that is exclusively directed to the infant's individual basic needs (e.g. the need of contact to parents by means of holding or skin-to-skin care).
- An important goal of pain management is to prevent pain; it is more difficult to try to control pain once it has recurred.
- All symptoms of distress and pain should be assessed regularly - ideally by means of a suitable and validated assessment scale.
- Depending on the current symptoms, non-pharmacological as well as additional pharmacological analgesic measures are provided to achieve optimal symptom control.
- The effectiveness of non-pharmacological and pharmacological measures can be further optimised by a general reduction of external stimuli such as light, noise, or cold stress.

2. Assessment of pain and distress

Since the late 1980s, more than 40 different assessment scores for acute, procedural pain in newborns have been validated and published [3]. However, acute, procedural pain is not a priority in palliative neonatal care. Rather, prolonged/chronic pain is the most frequent and challenging condition in the context of palliative care. For prolonged/chronic pain, only three pain scores are currently validated for neonates:

- Echelle Douleur Inconfort Nouveau-Né scale (EDIN scale) [4].
- Neonatal Pain, Agitation and Sedation Scale (N-PAS scale) [5,6].
- COMFORTneo scale [7].

However, all so-called “pain scales” are not specific for pain [8]. High scores may represent pain as well as distress caused by hunger,

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agitation, or the desire for physical closeness. It would be more correct to speak of “distress” scales in general rather than “pain” scales. Consequently, elevated pain scores in a newborn baby should always be interpreted in the clinical context by the medical team. Whenever possible, further assessments by other team members (e.g. physiotherapists), but also by the infant's parents, should be considered. Finally, it should be noted that so far no neonatal pain scale has been explicitly validated for use in patients under palliative neonatal care.

3. Non-pharmacological interventions

3.1. Behavioural and physical strategies

Various non-pharmacological measures can be used in neonates to reduce stress reactions in *acute procedural* pain [9,10]. Behavioural (e.g. swaddling, facilitated tucking) and physical (e.g. kangaroo care, breastfeeding, non-nutritive sucking) strategies have been shown to significantly reduce physiological and behavioural pain reactions of newborns after acute procedural pain [11]. The combination of several non-pharmacological measures is superior to the isolated use of non-pharmacological measures with regard to the pain modulating effect [12]. The use of non-pharmacological measures should be a consistent part of the daily care of newborns receiving palliative care. Within the framework of non-pharmacological measures, there is a valuable opportunity to actively involve parents in a central and essential aspect of their infant's care, namely pain and distress management.

3.2. Sucrose for analgesia

The soothing and pain-modulating effects of orally administered sugar on infants have long been known and the use of sugar substances was accordingly already an integral part of traditional infant care in the past. Today administration of oral sucrose in combination with and without non-nutritive sucking is the most frequently studied non-pharmacological intervention for *acute procedural* pain relief in neonates [13]. Sucrose is effective for reducing procedural pain scores from single events such as heel lance, venepuncture and intramuscular injection in both preterm and term infants but does not alter nociceptive brain activity [14]. No serious side effects or harms have been documented with this intervention. The pain modulating effect after oral administration of sucrose is superior to the isolated use of non-pharmacological measures in almost all studies. The effect of various non-pharmacological measures can be increased by the additional administration of sucrose/glucose. It is therefore recommended - whenever possible - to combine non-pharmacological measures with oral sucrose [15].

4. Pharmacological pain management

No analgesics with proven efficacy and safety other than opioids are currently available for the systemic treatment of severe pain in neonates. Dosing regime and route of administration of drugs used in palliative neonatal care are summarised in Table 1.

4.1. Opioids

In newborn infants, there is a high intra- and inter-individual variability in the metabolism of most opioids. For this reason, it is not possible to provide general or weight-related standard and/or maximum dosages, regardless of the type of application used. The dose of opioids required for optimal symptom control must be titrated individually to the effect. The required dose must be adjusted repeatedly if tolerance develops during the course of therapy. Of note, acute, painful procedures such as capillary blood collection [16] or endotracheal suction [17] are not treated sufficiently by opioids in preterm infants. Especially in premature infants, it is therefore advisable to apply non-pharmacological measures in combination with oral sucrose as a supplement to treat procedural pain, even during on-going continuous opioid infusion.

4.1.1. Routes of opioid administration

Parenteral. Intravenous administration of opioids has the advantage of rapid onset of the analgesic effect, simple dosage titration at the beginning of long-term therapy, and high and uniform bioavailability. The following aspects are to be considered if opioids are applied parenterally:

- Prolonged pain should be treated by continuous intravenous opioid infusion to ensure stable plasma levels and avoid under- or over-treatment due to fluctuating plasma levels.
- Bolus injections of opioids in newborns should only be used at the beginning of long-term therapy for initial loading and for the treatment of breakthrough pain.
- Opioid bolus injections should be administered as a short infusion over a period of approximately 5–10 min to prevent adverse effects such as severe arterial hypotension (especially in premature infants), laryngospasm, or severe thoracic rigidity.

Oral. In palliative care any medication should be administered in the simplest, safest, most effective and least unpleasant way. If no (central) venous access is in place, oral morphine solution can be used alternatively to opioid infusions. Following oral dosing, morphine has a significant first-pass effect in the liver. An oral-to-parental potency ratio of approximately 3:1 is commonly encountered during chronic administration.

Intranasal. In palliative neonatal care, intranasal drug administration is an alternative option for delivering opioids to patients without vascular access (off-label use). Most study data for intranasally applied opioids in the pediatric setting is currently available for fentanyl [18]. There is currently only one publication on the use of intra-nasal fentanyl for symptom control in palliative care in newborns and infants up to 6 months old [19], demonstrating that the use of intranasal fentanyl is safe and effective. Recommended single doses are 1–3 μg/kg, leading to a therapeutic effect within 5–10 min. The standard fentanyl injection solution (0.1 mg/2 ml) can be used for intranasal administration. Application by means of a mucosal atomisation device (MAD) as used in older children is not practicable for newborns as the volumes applied are too small. Intranasal fentanyl appears to be particularly suitable for symptom control in newborns cared for under palliative care immediately after birth in the delivery room.

For intranasally applied sufentanyl, only a few pediatric series with a small number of cases have been published so far, and for all other opioids no data on intranasal administration are available.

Subcutaneous. Subcutaneous administration of opioids can be an alternative to parenteral administration in newborns who cannot receive oral or intranasal opioid therapy. Subcutaneous opioids can be administered both as bolus for acute pain and as continuous infusion for prolonged/chronic pain. A commercially available intravenous cannula (24 or better 26 G) or a special subcutaneous cannula can be used for infusion access. The subcutaneous access should be exchanged every 48–72 h.

Rectal. The rectal administration of opioids is viewed with caution, due to the high variability of rectal absorption. It may be useful in the home care of the dying infant when no other route is available.

Transdermal. The transdermal application of fentanyl or buprenorphine in chronic and stable pain conditions is increasingly used in pediatric palliative care [20] while there are no reports in newborns. In our experience, the use of an opioid patch is feasible in neonates in selected individual cases when considering the following aspects:

- Opioid patches should only be used when symptoms of pain are stable.

Table 1
Dosing regime and route of administration of drugs used in neonatal palliative care.

	IV bolus	IV continuous	subcutaneous	oral	per rectum	intranasal	buccal
Morphine	0.05–0.1 mg/kg every 3–6 h	loading dose: 0.05–0.1 mg/kg starting dose: 0.01–0.02 mg/kg/h	For bolus und continuous infusion: see IV dosing regime	0.1–0.2 mg/kg every 3–6 h	0.1–0.2 mg/kg every 3–6 h	–	0.1–0.2 mg/kg every 3–6 h
Fentanyl	2–3 µg/kg every 1–4 h	loading dose: 2–3 µg/kg starting dose: 1–2 µg/kg/h	For bolus und continuous infusion: see IV dosing regime	–	–	1–2 µg/kg every 1–4 h	1–2 µg/kg every 1–4 h
N-Methylnaltrexone	0.15 mg/kg every (12-) 24 h	–	0.15 mg/kg every (12-) 24 h		–	–	–
Acetaminophen	7.5 mg/kg every 6 h	–	–	–	–	–	–
Esketamine	0.5–1 mg/kg* (e.g. for breakthrough pain)	loading dose: 1 ml/kg starting dose: 0.2–0.5 mg/kg/h	For bolus und continuous infusion: see IV dosing regime	2–4 mg/kg* (e.g. for breakthrough pain)	2–4 mg/kg* (e.g. for breakthrough pain)	2–4 mg/kg* (e.g. for breakthrough pain)	2–4 mg/kg* (e.g. for breakthrough pain)
Midazolam	0.05–0.1 mg/kg every 2–4 h	loading dose: 0.05–0.1 mg/kg starting dose: 0.1–0.2 mg/kg	For bolus und continuous infusion: see IV dosing regime	0.1–0.3 mg/kg every 2–4 h	0.1–0.3 mg/kg every 2–4 h	0.1–0.3 mg/kg every 2–4 h	0.1–0.3 mg/kg every 2–4 h
Phenobarbital	5 mg/kg every 24 h	–	–	5 mg/kg every 24 h	5 mg/kg every 24 h	–	–
Clonidine	–	0.5–2.5 µg/kg/h	–	2–4 µg/kg every 4–6 h	–	–	–
Dexmedetomidine	–	loading dose: 0.5 µg/kg starting dose: 0.3–1.0 µg/kg/h	–	–	–	–	–

Abbreviations: IV, intravenous.
Note: off-label use and off-label-route administrations are not shown separately.
* Esketamine: single doses can be used for e.g. *short time* painful procedures or acute breakthrough pain.

- Possible pain peaks (e.g. during re-positioning, endotracheal suction, etc.) are not covered by the opioid patch, necessitating additional measures.
- In newborns, use of the smallest fentanyl patch size (25 µg/h) available is recommended. In the case of a newborn weighing 3 kg, for example, 1/4 of the fentanyl patch (fentanyl patches can be cut) is then applied to the skin of the child, which corresponds to a fentanyl release of approximately 6 µg/h (or in this case 2 µg/kg/h).
- Fentanyl blood levels rise slowly when using transdermal application. Adequate analgesia can be achieved approximately after 12–24 h, and a steady state is reached 24–72 h after application of the patch.
- After removal of the patch, the effect fades slowly (approximately 12–18 h after removal). The skin area employed should remain free of new patches for 7 days afterwards.

4.1.2. Antagonisation of opioid side effects

Clinically significant side effects of opioids in newborns under palliative care include inhibition of intestinal motility via peripheral µ-receptors and urinary retention. Other side effects such as respiratory depression, thoracic rigidity, laryngospasm, hypotension and bradycardia play a minor role in the palliative context. Therapy approaches for the prevention or treatment of opioid-induced side effects show a very variable success in practice. In adult patients the opioid receptor antagonists, naloxone and methylnaltrexone are used increasingly to specifically antagonise opioid-induced side effects. Overall, no sufficient study data are available for the neonatal age for prophylaxis and treatment of side effects under opioid therapy.

Naloxone. Naloxone acts as a competitive, pure antagonist at central and peripheral opioid receptors. It can thus antagonise opioid-induced side effects mediated via peripheral opioid receptors. However, since naloxone crosses the blood-brain barrier, it also antagonises opioid-induced central analgesia. There have been several attempts in the past to treat opioid-induced side effects by systemic co-medication of low-dose naloxone. Published reports lack sufficient homogeneity to allow for any conclusions to be drawn. At higher doses (> 1 µg/kg/h), antagonisation of the central nervous system analgesic opioid effect must be expected. This adverse effect has even been described in a study on the use of orally administered low-dose Naloxone [21].

Peripherally Acting, µ-Opioid Receptor Antagonists (PAMORAs). Peripheral opioid receptor antagonism using substances from the class of PAMORA (Peripherally Acting, µ-Opioid Receptor Antagonist) represents a promising therapeutic concept. PAMORAs have restricted ability to cross the blood-brain barrier because of their polarity and low lipid solubility. Thus, PAMORAs cannot antagonise the opiate-induced central analgesia but can specifically block peripheral opioid receptors. To date only a few case reports on the use of the PAMORA N-methylnaltrexone in children - two of them in neonates (off-label use) [22,23] - and three smaller case series have been published. In selected individual cases we use a subcutaneous or intravenous single dose of 0.15 mg/kg N-methylnaltrexone for newborns with opioid-induced urinary retention or constipation/subileus (off lable use). If the treatment was successful after the first application and when the opioid-induced symptoms persist, we repeat the administration after 12–24 h at the earliest. Comparable to study results from adults, our limited anecdotal impression is that a response in about half of the patients can be expected.

There are currently no published reports on the use of orally administered PAMORAs (for example, naloxegol) in children.

4.2. Non-opioid analgesics

Currently, there is insufficient scientific evidence on analgesic efficacy or safety for the use of acetaminophen, non-steroidal anti-inflammatory drugs (NSAID), ketamine or transdermally administered local anaesthetics in neonates. However, as these drugs are administered in “eminence- and experience-based” practice not only in children but also in newborn infants, some information concerning these substances will be provided.

4.2.1. Acetaminophen (paracetamol)

Oral and rectal. All randomised placebo-controlled studies published to date did not demonstrate any analgesic effect of acetaminophen after rectal or oral administration in newborns. Even when using high dose regimens (single dose up to 40 mg/kg), they were not superior to placebo in terms of measured pain reduction. There is currently no evidence of justified routine use of oral or rectal acetaminophen as monotherapy or in combination with opioids for analgesia in newborns [24].

Parenteral. The first randomised, placebo-controlled double-blind study for parenteral use of acetaminophen in newborns (> 36 weeks of pregnancy) and infants (maximum age 365 days of life) was published in 2013 [25]. In this study a morphine-saving effect of acetaminophen (opioid co-administration, 30 mg/kg/d intravenous in 4 single doses) during the first 48 h after surgery could be demonstrated. In addition, Härma et al. [26] showed a morphine-saving effect of parental administered acetaminophen also in premature babies under 32 weeks of gestation.

4.2.2. Non-steroidal, anti-inflammatory (NSAID) agents

NSAIDs theoretically represent an interesting alternative to opioid therapy for mild to moderate pain. In particular, the potential avoidance of opioid-induced respiratory (apnoea), gastrointestinal (ileus) and uro-dynamic (urinary retention) side effects would be of high clinical relevance. At present, however, there is insufficient evidence on analgesic efficacy for the use of NSAIDs as analgesics in newborns. Attention must be paid in all patients with kidney function impairment if an individual decision is made to start treatment with a NSAID as part of palliative neonatal care. NSAIDs are capable of significantly inhibiting prostaglandin-dependent renal function in newborns. In the case of impaired kidney function, which leads to additional strain on the child, for example via over-hydration, a dose reduction of the NSAID may be sufficient in some cases, but often the treatment must be discontinued completely.

4.2.3. Esketamine

There are few studies on the efficacy and safety of esketamine in children treated for acute painful procedures. For newborns, only a few case reports and smaller case series on isolated individual doses of esketamine have been published, but no randomised, placebo-controlled studies that have investigated the efficacy and safety of prolonged esketamine therapy. Within the framework of palliative care, esketamine can be helpful in individual patients with pain that has responded poorly to the usual measures of opioid dose escalation and other adjuvants. We usually start an intravenous long-term therapy with a loading-dose 1 mg/kg slow push (10–15 min), followed by continuous infusion at a rate of 0.2 mg/kg/h and titrate up to approximately 0.5 mg/kg/h. Tolerance development may also occur under esketamine, so an increase in dose may be necessary in the course of the disease.

Esketamine can also be administered orally, subcutaneously, rectally and intranasally in the palliative care setting (off label use). Bioavailability after oral administration is very low at 15–20% due to a pronounced first-pass effect, therapeutic plasma levels being only reached after 20–30 min after oral administration. Subcutaneous bolus injections should always be applied as short infusions, otherwise pain and tissue damage may occur at the injection site. Subcutaneous long-term therapy using an infusion pump is also possible. The intranasal application is only suitable for bolus administration (start of anaesthesia approximately 5–10 min after application).

4.3. Regional anaesthetics

4.3.1. Infiltration anaesthesia

Local anaesthetics can be used for managing severe painful skin-breaking interventions (e.g. thoracic drainage, biopsies or punctures). Lidocaine (maximum dose 7 mg/kg), levo-/bupivacaine (maximum dose 2–3 mg/kg) and ropivacaine (maximum dose 3–4 mg/kg) are suitable local anaesthetics for use in neonates.

4.3.2. Transdermal application (ointment/cream/plaster)

The transdermal use of local anaesthetics in the form of a cream is widespread in pediatrics, effectiveness and safety having been proven for children 5 years and older. An analgesic effect in peripheral and central venepuncture, intramuscular injection and lumbar puncture was observed also in infants as young as 3 months. For infants under the age of 3 months, there are little data on effectiveness and safety.

4.3.3. Peripheral or central nerve blocks

Peripheral and central regional anaesthesia procedures have also enjoyed increasing popularity in recent years in the peri-operative care of newborns. These procedures are effective and safe in the hands of the experienced physicians. However, these “acute” techniques play only a minor role in palliative neonatal care.

5. Sedation in palliative neonatal care

In addition to adequate pain therapy, palliative care also includes the consistent prevention and treatment of other distress such as restlessness and agitation. In spite of minimization of noise, light, sleep disturbances, and other negative stimuli for the infant, pharmacological sedation is often indispensable, especially in end of life situations. In general, the targeted level of sedation should be the lowest that relieves distress. Conscious sedation, where the infant is calm and able to interact with her or his parents, is often considered the ideal level of sedation. In case of intense distress, severely refractory symptoms, or anticipated death within hours, continuous deep sedation may be indicated. In the absence of controlled trials evaluation sedatives in palliative neonatal care, the drug choice is largely empirical. Medications widely used to deliver sedation in palliative neonatal care are: opioids, benzodiazepines, barbiturates, and fairly recently alpha2-adrenoreceptor agonists.

5.1. Opioids

While opioids are often used expressly for their sedating properties in acute neonatal intensive care situations (e.g. in postoperative care), they are not very effective in producing reliable, prolonged sedation in severely distressed infants under palliative care. In these challenging situations we recommend combining opioids with specific sedatives such as benzodiazepines. For further information on opioids see 4.1.

5.2. Midazolam

Midazolam was one of the first benzodiazepines reported to be used for sedation in palliative care. It has a rapid onset and short duration of action, facilitating titration. Parental sedation with midazolam is recommended to be started with a loading dose of 0.05–0.1 mg/kg, followed by continuous infusion of 0.1–0.2 mg/kg/h. However, especially in the non-hospital setting oral, rectal, intranasal, or subcutaneous application of midazolam may be indicated.

5.3. Phenobarbital

Phenobarbital may be used alternatively to midazolam. In the context of sedation in palliative neonatal care phenobarbital should be given preferably orally (5 mg/kg/d), as absorption is slow, therefore severe side effects are not to be expected.

5.4. alpha2-adrenoreceptor agonists

Applied systemically, alpha2-adrenoreceptor agonists have a sedative and anxiolytic effect. In pediatrics, they are used for pre-medication before surgery, for symptomatic therapy in opioid withdrawal, for sedation in mechanically ventilated patients or ahead of invasive procedures. Very little data is available on the use of alpha2-adrenoreceptor agonists in neonates [27,28]. The studies available so far prove a sedative effect also in newborns. Clonidine and dexmedetomidine are thought to be safer than opioids with regard to their acute side effect profile. In distressed, agitated newborns treatment with clonidine or dexmedetomidine can therefore be considered in individual cases (off label use). Side effects of alpha2-adrenoreceptor agonists include bradycardia, hypotension and oliguria/anuria caused by a decrease in renal perfusion.

6. Special aspects of symptom control

6.1. Compassionate extubation

Particularly in newborns, in whom a relevant period of spontaneous self-breathing can be expected after compassionate extubation, careful preparation is necessary in order to be able to counteract in a prophylactic manner potentially occurring distressful symptoms. The main objectives of palliative care of a neonate in the context of compassionate extubation should therefore be:

- Anticipation of pain and terminal agitation as well as prophylactic or rapid treatment thereof.
- Prevention or rapid therapy of dyspnoea (mostly caused by stridor after extubation or rarely by excessive broncho-pulmonary secretion after long-term ventilation).

Agitation and pain can significantly increase the work of breathing after mechanical ventilation and compassionate extubation. In the course of this, physical exhaustion can occur, which means additional distress for the dying child. Consistent analgesia and sedation can counteract this and should therefore have the highest priority. Opioid therapy to prevent pain and distress caused by acute dyspnea should be started before withdrawal of mechanical ventilation and compassionate extubation. Benzodiazepines may be used as anxiolytics or as an adjuvant to an opioid analgesic. Opioids and benzodiazepines appear paradoxically to not hasten inevitable death after ventilator withdrawal [29].

Neuromuscular blocking agents (NMBAs) feign freedom from pain and inner peace, the risk of under-treatment with analgesics and/or sedatives in relaxed patients being very high [30]. Having these risks in mind, there are very limited conditions in which the use of NMBAs can be reasonable. NMBAs should never be used as a sole agent and deep analgo-sedation should be warranted. Sometimes NMBAs are continued for compassionate extubation with the goal of preventing gasping at the end of life. Gasping is a physiological process (‘reflex’) that occurs to varying degrees in every natural dying process. According to current knowledge, terminal gasping is not associated with distress and it cannot be prevented by the application of opioids or sedatives.

In very rare exceptional cases after discontinuation of ventilation excessive respiratory secretion can occur in newborn infants. Post-extubation stridor can give rise to the parents' perception that their child is choking and suffering. The following measures can be considered to address these distressing symptoms [31]. Six hours before compassionate extubation, enteral feeding should be stopped and parenteral fluids reduced, overhydrated patients should be dehydrated with furosemide. At the same time administration of sedatives (for distress) and opioids (for pain and/or dyspnea) should be continued or started. Especially in

neonates with previous episodes of a stridor after extubation, methylprednisolone should be given in anticipation of stridor after extubation.

Hypoxia acts as an additional “natural sedative”. We therefore reduce oxygen supplementation to FiO2 0.21 before terminating mechanical ventilation and generally do not use oxygen supplementation after compassionate extubation.

6.2. Withdrawing artificial nutrition and hydration

In neonatal intensive care withdrawal of life-sustaining treatment consists predominantly of withdrawal of assisted ventilation or pharmacological support for the cardiovascular system. However, when critically ill newborns ‘linger’ after withdrawal of life-sustaining intensive care treatment, with continued neurological impairment and poor long-term outcome, the withdrawal of artificial nutrition and hydration may become a consideration [32]. Although the practice is emerging as an accepted part of palliative care in adults, withdrawal of artificial nutrition and hydration is a significant challenge for practitioners in neonatal medicine [33].

Studies in adults have shown that death after withdrawal of artificial nutrition and hydration is not caused by starvation but by dehydration. Dehydration in end of life situations leads to a reduction in nausea, vomiting, diarrhoea and urine production, which is associated with less distress [34,35]. Furthermore, parenteral nutrition and hydration in end of life situations often contributes more to the increase in suffering (e.g. pulmonary oedema caused by fluid overload can cause severe shortness of breath). The distressing feeling of thirst does not correlate with the amount of fluid supplied but with the degree of dryness of the oral mucosa. In conclusion, continuing artificial nutrition and hydration in many neonates receiving palliative care may not always be the patient’s best interest and therefore not indicated, while treating thirst through adequate oral care is always necessary. Liberal use of analgesics (opioids) and sedatives (benzodiazepines) in addition to sufficient oral care should prevent most distressing symptoms. In a retrospective study by Hellmann et al. [36], the median time to death after discontinuation of parenteral nutrition and fluid intake in newborns was 16 days (minimum 2 to maximum 37 days).

However, as long as a newborn with a life-limiting condition likes to be fed orally, enteral nutrition should not be stopped [37].

Practice points

- Prevention of pain and distress is the most effective way of successful pain and distress management. In palliative neonatal care all diagnostic and therapeutic measures should be reviewed carefully for the following question: Do they improve the patient's quality of life?
- Regular distress and pain assessment by means of an assessment scale should be guaranteed for all neonates receiving palliative care.
- Depending on the current symptoms, non-pharmacological as well as pharmacological analgesic measures are provided to achieve optimal symptom control.
- The effectiveness of non-pharmacological and pharmacological measures can be further optimised by a reduction of external distressing stimuli (e.g. light, noise, or cold stress).
- Within the framework of non-pharmacological measures, parents should get the opportunity to be involved in pain and distress management (e.g. by providing comforting touch).
- Anticipation and consistent treatment of pain and distress are essential when withdrawing mechanical ventilation or artificial nutrition and hydration.

Research directions

- Clinical reliability and validity of existing assessment tools for pain (and/or distress of other sources) in neonates receiving palliative neonatal care. Is there a need for adaption of assessment tools for pain/distress when used in palliative neonatal care? Do we need new assessment tools for pain/distress in these challenging situations?
- Improving knowledge about efficacy and safety of (non-opioid) drugs such as ketamine, NSAID, or acetamoniphen when used in neonatal palliative care situations.
- Observational studies inquiry into pain and distress management in special palliative neonatal care situations [e.g. end-of-life care (i) in the delivery room, (ii) at the limits of viability, (iii) after compassionate extubation, or (iv) after withdrawal of artificial nutrition and hydration].

Conflicts of interest

There are no conflicts of interest to report.

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