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Managing neonatal pain in the era of non-invasive respiratory support

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ABSTRACT

Non-invasive ventilation is currently the preferred respiratory support for premature infants with respiratory distress. The lung-protective effects of non-invasive ventilation should however not prompt disregard for the possible pain and discomfort it can generate. Non-pharmacological interventions should be used in all premature infants, regardless of their respiratory support, and are not detailed in this review. This review includes currently available evidence and gaps in knowledge regarding three aspects of pain management in premature infants receiving non-invasive ventilation: optimisation of non-invasive ventilation especially through the choice of positive pressure source, appropriate interface and synchronisation; sedative or analgesic drug use for strategies aiming at administering surfactant with reduction or avoidance of tracheal ventilation; risks and benefits of some analgesic and/or sedative drugs used to treat or prevent prolonged pain and discomfort during non-invasive ventilation. In spite of limited robust evidence, this overview should trigger caregivers' reflections on their daily practice.

1. Introduction

Non-invasive ventilation (NIV) is preferred to invasive ventilation in premature neonates as it is associated with increased survival without bronchopulmonary dysplasia [1]. Unlike patients from other age groups, premature neonates can thus receive uninterrupted NIV during their hospital stay for prolonged periods that can last for weeks or even months for the most immature infants [2]. But NIV can cause discomfort or even pain, especially through nasal injury [3], which can compromise the efficacy of NIV itself. In addition, optimising the comfort and pain management of these babies is mandatory, not only to improve the efficacy and tolerance of their respiratory support, but also to preserve their later neurodevelopmental outcome [4]. Non-pharmacological strategies to reduce pain and improve comfort in the neonatal intensive care unit (NICU) have been reviewed elsewhere [5] and should be implemented for babies receiving NIV. The first part of this review will specifically focus on the devices and interfaces used during NIV for premature infants and their impact on comfort and pain.

In order to further reduce tracheal ventilation, several strategies have been proposed to deliver surfactant. First, the "Intubation-surfactant administration – immediate extubation" (INSURE) technique has been used for several years and requires specific premedications to allow rapid extubation. Second, strategies to deliver surfactant without endotracheal intubation have recently emerged including "less invasive surfactant administration" (LISA) or "minimally invasive surfactant treatment" (MIST) and laryngeal mask use [6]. These techniques probably have a positive effect on respiratory morbidity [6,7], and are rapidly spreading in some countries [8]. However, sedation or analgesia are rarely used to perform these procedures [8]. Since LISA or MIST require laryngoscopy, a known painful procedure, their performance without sedation and/or analgesia might be considered as a regress compared to endotracheal intubation, for which such treatments are recommended [9] and usually given [10]. Thus, the second part of this review will provide a synthesis on the efficacy and tolerance of premedication regimens used for surfactant administration using the INSURE technique, LISA/MIST techniques or laryngeal mask.

Finally, the daily care of these babies is extremely challenging since their respiratory disease and immature central respiratory command expose them to frequent apnoea and desaturations. Therefore, any intervention aimed at improving their comfort should avoid respiratory depression, which makes difficult the use of most sedative, analgesic or anaesthetic drugs. Thus, the last part of this review will focus on pharmacological treatment in infants receiving NIV.

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2. Improving comfort during non-invasive respiratory support

2.1. Role of NIV system: continuous positive airway pressure (CPAP) versus heated and humidified high flow nasal cannula (HFNC)

Several randomised controlled trials have compared CPAP with HFNC in premature infants with respiratory distress to assess their respective efficacy in treating respiratory distress syndrome after birth or in preventing extubation failure [11]. The systematic review and meta-analysis performed by Wilkinson et al. did not find any obvious difference in studied outcomes between HFNC and alternative NIV strategies, except for a reduction in nasal trauma associated with HFNC (risk difference (RD) −0.14, 95% CI -0.20 to −0.08) [11]. However, the alternative NIV strategies included various systems, devices and interfaces that complicate the interpretation of results.

A systematic review assessing nasal injury during NIV in premature infants found incidences ranging from 20% to 100% and confirmed the reduction in nasal injury with the use of HFNC as compared to CPAP (RD - 0.14, 95%CI -0.17 to −0.10), although important heterogeneity between studies was noted [3].

Two studies have more specifically assessed infants' comfort and/or pain as a primary outcome by comparing HFNC and CPAP [12,13]. In a cross-over study, Klingenberg et al. assessed pain using a cumulative EDIN pain score [14] (sum of 3 assessments) in 20 premature infants (mean (SD) gestational age, 29.3 (1.7) weeks; median (IQR) postnatal age, 6 (4–10) days) who were assigned to two 24 h periods of ventilation with variable flow CPAP or HFNC in a random order [12]. The cumulative EDIN score was around 11 in both groups (meaning a mean score below 4 for each of the three assessments), without any significant difference between groups, which suggests that both ventilatory devices resulted in acceptable comfort in this study. Since the sample size calculation was based on the assumption that the cumulative EDIN score in the CPAP group would be 16 and that a 25% reduction (i.e. EDIN score = 12) would be observed in the HFNC group, it is possible that the study was underpowered, as mentioned by the authors [12].

An observational cross-sectional study assessed pain using the premature infant pain profile (PIPP) [15] in 60 subjects supported with CPAP or HFNC [13]. In this study, infants had a median gestational age of 32 weeks and a median postnatal age of 5–6 days. The PIPP score was calculated by trained nurses who watched videos (45 s) and who were not informed of the nature of the study. In this study, Osman et al. reported a significant decrease in PIPP scores in the HFNC group versus the CPAP group (respectively 4 (2–6) and 10 (7–12), p = 0.01). No infant in the HFNC group had a PIPP score > 12 (the admitted threshold for severe pain) versus 5/37 (13.5%) in the CPAP group (p = 0.03). It is however interesting to note that 7/23 (30.4%) infants from the HFNC group and 19/37 (51.4%) infants from the CPAP group had scores between 6 and 12, which indicates mild to moderate pain. Although their study had limitations, Osman et al. objectively demonstrated the possible painful effect of these two non-invasive devices in premature infants, in the absence of other painful procedure or nasal injury (non-inclusion criteria) [13].

In summary, the evidence is not sufficient to recommend HFNC use over CPAP, however it should be strongly considered in babies at risk of nasal injury and in babies showing signs of discomfort while receiving CPAP.

2.2. Role of NIV interface

In addition to the elevated number of devices available to provide NIV, there is an even larger number of interfaces to be placed on the infants' face [16]. If binasal prongs are more effective than single nasal/nasopharyngeal prongs in reducing the rate of re-intubation [17], no consensus exists to date concerning the type of binasal prongs or mask that should be preferentially used. RAM nasal cannulae have also been proposed as an alternative to binasal prongs or masks [18]. When choosing a specific interface for an infant, caregivers should consider both the efficacy and the tolerance of the selected device. Since the status of these infants is rapidly changing, it seems misleading to think that a specific interface will meet the needs for all babies. However, some studies have specifically assessed the comfort of different interfaces used for NIV in premature infants.

In a secondary analysis of an open labelled, multi-centre, randomised, controlled trial, Khan et al. assessed nasal injuries and pain using the N-PASS scale [19] in 170 premature infants who received either Jet CPAP with dedicated prongs or bubble CPAP with two types of short binasal prongs: Fisher and Paykel's prongs (Healthcare, New Zealand) or Hudson prongs (Hudson Respiratory Care Inc., Temecula, California, USA) [20]. Nasal injury was observed in 36/80 (45%) infants from the Jet CPAP group *versus* 67/90 (74%) for the bubble CPAP group (relative risk 0.6, 95% CI 0.5 to 0.8). Neonates in the Jet CPAP group had significantly lower average (median (IQR): 3 (8, 13) vs. 4 (8, 14); p = 0.04) as well as maximum N-PASS pain score (median (IQR): 4 (8, 14) vs. 5 (13, 16); p = 0.01) in comparison to the bubble CPAP group.

A systematic review assessed different strategies to prevent or reduce nasal injury in premature infants receiving NIV [3]. Pooled analysis identified the use of nasal barrier dressing (RD -0.12, 95%CI -0.20 to −0.04), as well as the use of nasal mask rather than binasal prongs (risk ratio 0.80, 95%CI 0.64 to 1.00) as potentially useful strategies to prevent nasal injury [3]. In line with these conclusions, a randomised controlled trial demonstrated that the use of nasal barrier dressing significantly reduced nasal injury during binasal NIV: nasal injury was observed in 18/53 (34%) infants in the barrier group vs 31/55 (56%) in the no barrier group (p = 0.02) [21]. The reduction in severe nasal injury with nasal mask was also reported in another meta-analysis (risk ratio 0.41, 95% CI 0.24 to 0.72), in addition to a significant reduction in CPAP failure (risk ratio 0.63, 95% CI 0.45 to 0.88) as compared to binasal prongs [22].

The RAM cannula was assessed in a limited number of studies. In a single-centre prospective observational study, it was used in infants receiving CPAP or nasal intermittent positive pressure ventilation (NIPPV) with skin breakdown or discomfort/agitation [18]. Although comfort or pain was not assessed in this study, Nzegwu et al. reported that there were no new instances of nasal breakdown or injury with RAM nasal cannula use [18]. In another prospective observational study, the rate of nasal injury was significantly decreased with the use of RAM cannula, as compared to a historical control group: 3/36 (8%) in the RAM cannula group vs 19/36 (53%) in the control group (p < 0.01) [23].

In summary, nasal mask use probably reduces the risk of nasal injury without compromising CPAP. However, the use of a single interface is rarely feasible in practice and alternating interfaces may be helpful to change sites of constant pressure on the infant's face [3]. When using binasal prongs, the use of a nasal barrier dressing should be strongly considered. The use of RAM cannula might also be considered, provided that its efficacy is considered acceptable as compared to other interfaces.

2.3. Neurally adjusted ventilatory assist (NAVA)

NAVA is a ventilatory mode using the diaphragm electrical activity to deliver synchronised and proportional inspiratory pressure invasively or non-invasively [24]. In the pediatric ICU, mechanical ventilation with NAVA led to a reduction in sedation after excluding postoperative patients, as compared to conventional ventilation [25].

However in neonates, a randomised controlled trial using duration of ventilation as primary outcome found no difference in the cumulative dose of opiates used during conventional ventilation or invasive NAVA [26].

NIV with NAVA has been assessed in some studies, but none specifically assessed comfort or pain. In a crossover trial including 15

infants (median (IQR) GA, 27 + 1 (26 + 0–28 + 2) weeks; median (IQR) postnatal age, 25 (17.5–32) days), Lee et al. showed a significant improvement in synchronisation with NIV-NAVA as compared to NIV-pressure support (asynchrony index 19.7% *vs* 73.9%, $p < 0.001$) [27], which probably contributed to infants' comfort. In a pilot crossover trial conducted in seven infants (median (IQR) GA, 26.6 (25.2–26.6) weeks; median (IQR) postnatal age, 23 (19.5–36.5) days), Gibu et al. observed a significant reduction in the frequency of desaturations ($-42 \pm 12\%$, $p < 0.006$), the duration of desaturations ($-33 \pm 10\%$, $p < 0.01$), the infant movements ($-42 \pm 9\%$, $p < 0.01$) and caretaker movements ($-29 \pm 8\%$, $p < 0.01$) [28]. Altogether, these parameters might be a proxy for the infants' comfort that was not directly assessed in this study.

3. Use of analgesic and sedatives for surfactant administration without subsequent invasive ventilation

3.1. Intubation - surfactant administration - extubation (INSURE) technique

The INSURE technique aims at reducing the duration of invasive ventilation and is associated with less need for mechanical ventilation, lower incidence of BPD and fewer air leak syndromes [29]. Premedications used during the procedure have been reviewed in 2013 and the authors concluded that short-acting opioids (especially remifentanil) or propofol were suitable candidates, although evidence was insufficient to recommend a specific dosing or protocol [30]. Since then, a prospective study with remifentanil (cumulative doses ranging from 1 to 5 μg/kg) was prematurely interrupted because of poor sedation and frequent chest wall rigidity [31]. A dose-finding study on propofol as premedication before the INSURE procedure proved the feasibility of a titration strategy and recommended relatively low initial doses (0.7–1.4 mg/kg) with subsequent up-titration [32].

3.2. LISA/MIST techniques

LISA/MIST techniques are associated with reduced BPD as compared to invasive surfactant administration methods [7]. However, most published randomised trials did not use any premedication prior to laryngoscopy [2,33–36], although conscious laryngoscopy is undoubtedly painful and associated with adverse physiological reactions such as increased intracranial pressure [9]. The main characteristics and findings of clinical studies on LISA/MIST with or without sedation/analgesia are summarised in Table 1. Most studies using analgesia or sedation recruited infants around 29 weeks GA [37–40]. When compared to studies without premedication in the same GA group [33,36], the frequency of any mechanical ventilation before 72 h of life appeared higher. In addition, desaturations were very common in studies that used analgesic or sedative drugs (Table 1).

To date, one randomised controlled trial has compared 1 mg/kg intravenous propofol to no premedication before LISA, using the Comfortneo [41] score < 14 as primary outcome [39]. In this study Dekker *at al.* found a significant decrease in the rate of infants with a Comfortneo score < 14 in the propofol group as compared to the control (no premedication) group: 8/36 (22%) *vs* 32/42 (76%), respectively ($p < 0.001$) [39]. However, this improvement in pain control was at the expense of increased respiratory support (NIPPV) (93% *vs* 47%, $p < 0.001$) and more frequent desaturations during the procedure (91% *vs* 69%, $p = 0.023$) in the sedated group, without significant increase in the intubation rate within 24 h (24% vs 17%, $p = 0.58$).

Two previous observational studies already suggested the suitability of low dose propofol to perform LISA/MIST [38,40] and another observational study found a relatively high rate of subsequent intubation with the use of ketamine [37].

In summary, although low dose propofol seems promising, more research is required to find an optimal premedication regimen to

Table 1
Summary of studies on LISA/MIST with or without analgesia/sedation.

	Clinical trials without systematic analgesia/sedation					Clinical trials with analgesia/sedation			
Publication's reference	[34]	[35]	[36]	[33]	[2]	[38]	[40]	[37]	[39]
Study's design	RCT	RCT	RCT	RCT	RCT	Retrospective study	Retrospective study	Prospective study	RCT
Population	27.6 n = 108	28.0 n = 100	29.6 n = 66	29.1 n = 46	25.3 n = 107	29.0 n = 23	29.5 n = 35	30.0 n = 29	29.0 n = 42
Mean GA (weeks), N									
Premedication	At the discretion	None	Atropine	Not specified	Not specified	Propofol	Propofol titration	Atropine Kétamine titration	Propofol
				Probably none	*Probably none*	1 mg/kg	0.5 mg/kg	0.5 mg/kg	1 mg/kg
MV < 72 h	28%	30%	19%	17%	47%	35%	34%	41%	24%[a]
Tolerance	Nadir SpO_2 80 (70–87)	17% bradycardia and desat	4.5% desat	Not detailed	56%	100%	100% SpO_2 < 85%	58%	91%
					SpO_2 < 80%	SpO_2 < 80%		SpO_2 < 80%	SpO_2 < 85%
								> 60s	33% MABP < GA

Abbreviations: RCT, randomised controlled trial; GA, gestational age; MV, mechanical ventilation; desat, desaturation; MABP, mean arterial blood pressure.
[a] Use of MV within 24 h of the procedure.

perform LISA/MIST and this research is crucial in order to avoid conscious laryngoscopy, which should be limited to life-threatening situations [9].

3.3. Laryngeal mask

Three randomised controlled trials compared surfactant administration through laryngeal mask to endotracheal intubation [42,43] or CPAP alone [44]. None included premedication prior to laryngeal mask insertion and only one assessed pain/comfort as a secondary outcome. In this last study, Barbosa et al. found higher neonatal infant pain scales in the laryngeal mask group, compared to the intubated group who had received premedication with midazolam and remifentanil [43]. However, the median pain scores were comparable at baseline and after laryngeal mask removal.

In an observational study on surfactant administration through laryngeal mask, the video provided as a supplementary file (accessed at https://figshare.com/articles/Catheter_and_Laryngeal_Mask_Endotracheal_Surfactant_Therapy_the_CALMEST_approach_as_a_novel_MIST_technique/4263713) shows that the procedure can be uncomfortable, at least in some infants [45].

4. Use of pharmacological treatments during NIV

4.1. Experience in neonatal, pediatric and adult intensive care

The use of pharmacological sedation and/or analgesia during NIV is a controversial subject. Indeed, the main goal of sedation during NIV is to provide comfort and analgesia while ensuring minimal or absence of respiratory depression and impairment of the upper airway. The risk-benefit ratio has to be carefully outweighed when considering pharmacologic pain control and/or sedation in premature infants.

Recent recommendations advise to minimise stress and to prefer non-pharmacological analgesic techniques in neonates [46]. However, the use of analgo-sedative drugs is sometimes required and might even help in specific situations [47].

In the literature, around 20% of patients treated with NIV received pharmacological sedation or analgesia: 18% (266/1496) of neonates in a European prospective cohort (EUROPAIN) [48] and 19.6% (165/842) of adults in an international prospective cohort [49]. In both neonates and adults, intermittent sedation was preferred to continuous sedation [48,49]. Longrois et al. reviewed the use of sedation during NIV in adult patients: they advised against benzodiazepines use; opioids and propofol might also be deleterious during NIV due to increased collapsibility of the upper airway; dexmedetomidine and ketamine presented the most suitable pharmacological profiles [47]. In neonates, paracetamol (11%) was most frequently used, followed by opioids (6%), hypnotics (3%) and general anesthetics (< 1%) [48].

To our knowledge, there is no randomised clinical trial available assessing the use of analgo-sedation during NIV in neonates. An observational prospective study in 64 preterm neonates (mean (SD) GA, 29.6 (3.3) weeks; postnatal age, 10–13 days) under CPAP reported a significant decrease in heart rate, respiratory rate and pain scales after administering a single dose of morphine (25 ± 12 μg/kg) [50]. Six patients (9.3%) developed delayed apnoea requiring intervention: two received naloxone, two received pharyngeal ventilation, one was intubated and one received naloxone and was subsequently intubated. Patients born < 28 weeks had higher risk of severe apnoea [50]. Similarly, a retrospective matched-cohort study in non-intubated neonates undergoing central line placement reported a significant difference in respiratory depression between morphine-treated infants (mean (SD) dose, 60 (20) μg/kg) and controls (11.6% *vs* 0%, p = 0.02) [51].

Overall, the risks of morphine administration at doses of 10 μg/kg and higher outweigh the benefits of pain control. However, pain and discomfort induced by NIV cannot be ignored and pharmacological alternatives such as paracetamol or dexmedetomidine might be considered if needed.

4.2. Paracetamol

In an attempt to avoid opioids or sedatives, there is a trend towards increased use of paracetamol to deal with neonatal pain [52]. For example in the German Neonatal Network, 5.6% of very low birth weight infants received paracetamol in a 2003–2009 period versus 8.1% in 2010 [53]. To our knowledge, there is no specific study reporting the effect of paracetamol use on pain or discomfort related to NIV. More generally, there are few studies on paracetamol monotherapy in neonates and especially preterm neonates. In a recent Cochrane systematic review on paracetamol use in neonates [54], it has been shown to be a poor procedural analgesic (for heel lances or retinopathy screening). On the other hand, paracetamol has a sparing effect on morphine requirements for post-operative pain management in infants born > 36 weeks [55]. This sparing effect has also been suggested in infants born < 32 weeks GA hospitalised in the NICU [56].

Concerning safety paracetamol demonstrated a good short-term tolerance profile with modest hemodynamic adverse effects and prospective data suggested good hepatic tolerance [57]. Nevertheless, long-term outcomes need to be considered. Epidemiological studies suggested associations between perinatal paracetamol exposure and long-term outcomes. Indeed, it might have a role in the development of asthma and atopy, in impaired masculinisation and in neurobehavioral outcome such as attention deficit hyperactivity disorder incidence [58]. Some of these associations could reflect reverse causality or confounding but further studies are definitely needed.

In summary, evidence is lacking to support or discourage the use of paracetamol to improve comfort in neonates with NIV.

4.3. Dexmedetomidine

To obtain conscious sedation, dexmedetomidine has been more and more used in pediatric ICUs [59]. It exhibits valuable properties: it provides sedation, anxiolysis and analgesia with no significant respiratory depression and no direct effect on the patency of the upper airways [47].

A large retrospective cohort study by Venkatraman et al. reported the use of dexmedetomidine in 202 children receiving NIV [60]. Patients received doses ranging from 0.4 to 0.8 mcg/kg/h and were treated during a median of 35 h. The target sedation level was achieved in 168/202 (83%) of patients. This study was mainly conducted in children with status asthmaticus and bronchiolitis, with only 7.9% of patients < 6 months old and no mention of neonates. In another cohort of 382 pediatric patients receiving NIV, dexmedetomidine was used at a median dose of 1 mcg/kg/h and for a median time of 45 h with well-tolerated hemodynamic effects including bradycardia and hypertension [61].

Few studies have assessed the use of dexmedetomidine in neonates and assessment occurred mainly during mechanical ventilation. A phase II/III study conducted in 42 preterm and term neonates (GA ≥ 28 weeks, weight at inclusion ≥ 1 kg) assessed dexmedetomidine for sedation during mechanical ventilation with a loading dose (range 0.05–0.2 μg/kg) followed by a maintenance dose (range 0.05–0.2 μg/kg/h), both depending on gestational age [62]. A majority of patients were adequately sedated with only 9% requiring extra sedation and no significant adverse effects were observed. Twenty percent of patients were extubated while receiving dexmedetomidine and no major adverse event was reported in this study.

A retrospective case-control study in 48 premature neonates (mean GA 25 weeks, mean postnatal age 27 h) compared sedation with fentanyl or dexmedetomidine (mean infusion rate 0.6 μg/kg/h; mean duration 12 days) during mechanical ventilation. Patients in the dexmedetomidine group had a significantly higher percentage of treatment days requiring no additional sedation (54.1% *vs* 16.5%, p < 0.05) and

a shorter duration of mechanical ventilation (mean (SD) 14.4 (7.3) *vs* 28.4 (9.9) days, $p < 0.0001$) [63]. However, these outcomes probably reflect practices influenced by the drugs used, rather than the sole effects of each drug. In this study, dexmedetomidine infusion was not an obstacle to extubation and to spontaneous breathing since 83% of preterm neonates in the dexmedetomidine group were still receiving it at the time of extubation. There was no hemodynamic adverse effect (hypotension, hypertension or bradycardia) noted in the dexmedetomidine group and no sign of withdrawal.

Overall, dexmedetomidine could be a valuable tool for sedation during NIV in neonates. Studies addressing dexmedetomidine use in neonates are promising with an apparently good short-term tolerance in this population. However, these studies are not specific to neonatal NIV, do not address long-term outcome and contain data for a small number of patients. Hence, further efficacy and safety studies in neonates with NIV and on larger cohorts are required.

5. Conclusion

Overall, besides non-pharmacological strategies, very little robust evidence is available to guide clinical practice aiming at promoting comfort and pain control during NIV in premature infants. This underlines that unsatisfactory analgesia might be considered as the “price to pay” in order to maintain NIV. However, proper pain assessment should be systematically included in future trials dedicated to respiratory strategies because short-term respiratory benefits should not outweigh long-term adverse effects of early painful experiences. New approaches, such as nebulised surfactant or synchronisation of NIV cannot solely focus on respiratory outcomes. While results from future research are awaited, a pragmatic, common sense based approach seems reasonable in order to prevent or treat pain or discomfort in premature babies receiving NIV. Wisely choosing the best NIV delivery system and interface, improving synchronisation (or avoiding asynchrony) and parsimoniously using effective and safe analgesic and/or sedative drugs should be part of daily care in modern NICUs.

5.1. Practice points

- Non-invasive ventilation provides lung protection to premature infants with respiratory distress but it can cause pain and/or discomfort
- High flow nasal cannulas decrease the risk for nasal injury as compared to CPAP, but their respective efficacy is still debated.
- During CPAP, the use of nasal masks rather than nasal cannulas and the use of nasal barrier dressing for nasal cannulas decrease the risk for nasal injury.
- Although the effect of asynchrony during non-invasive ventilation on comfort/pain has not been assessed in premature neonates, neurally adjusted ventilatory assist improves synchrony and might improve comfort.
- Strategies currently used to avoid mechanical ventilation while administering surfactant have insufficiently studied the assessment and management of pain related to upper airway access.
- The use of opioids or benzodiazepines should be discouraged in premature infants receiving non-invasive ventilation.
- Paracetamol and dexmedetomidine are potential analgesic drugs in premature infants receiving non-invasive ventilation.

5.2. Research directions

- Currently used non-invasive respiratory support modes and interfaces should be specifically assessed for their impact on comfort and pain.
- Comparison of conventional CPAP with high flow nasal cannulas or non-invasive neutrally adjusted ventilatory assist should be performed with regard to prolonged pain and comfort.
- Propofol is a promising premedication for LISA/MIST and deserves further investigation.
- Efficacy, safety and short- and long-term and tolerance of paracetamol and dexmedetomidine to treat or prevent discomfort/pain during non-invasive ventilation should be studied in premature infants.

Conflicts of interest

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