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Evidence-based clinical guidelines on analgesia and sedation in newborn infants undergoing assisted ventilation and endotracheal intubation

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ABSTRACT

Aim

This review informed pain control guidelines for clinicians performing mechanical ventilation, nasal continuous positive airway pressure and endotracheal intubation on term and preterm newborn infants.

Methods

We reviewed literature published between 1986 and June 2017 on analgesia and sedation during assisted ventilation and before endotracheal intubation in newborn infants admitted to neonatal intensive care units. The subsequent guidelines were developed using the Grading of Recommendations Assessment, Development and Evaluation approach.

Results

Our review produced five strong standard of care recommendations. One, reduce neonatal stress and use non-pharmacological analgesia during invasive ventilation. Two, favour intermittent boluses of opioids, administered after pain scores and before invasive procedures, during short expected periods of mechanical ventilation, mainly in preterm infants affected by respiratory distress syndrome. Three, do not use morphine infusion in preterm infants under 27 gestational weeks. Four, always use algometric scores to titrate analgesic drugs doses. Five, use premedication before endotracheal intubation for a more rapid, less painful, less traumatic and safer manoeuvre. We also developed 30 conditional recommendations on therapeutic options.

Conclusion

Our review produced 35 recommendations on standard care and therapeutic options relating to the analgesia and sedation of newborn infants during ventilation and before endotracheal intubation.

KEY NOTES

- This review examined literature published between 1986 and June 2017 on analgesia and sedation during assisted ventilation and before endotracheal intubation in newborn infants admitted to neonatal intensive care units.
- Five strong standard of care recommendations were developed after the research was assessed using the Grading of Recommendations Assessment, Development and Evaluation approach.
- This process was also used to develop 30 conditional recommendations on therapeutic options.

Keywords: Continuous positive airway pressure, Endotracheal intubation, Guidelines, Mechanical ventilation, Neonatal pain.

INTRODUCTION

Endotracheal intubation is a stressful, painful and potentially dangerous procedure because it can impair vital functions and cause trauma to the airways. Premedication of endotracheal intubation with sedatives, analgesics and muscle relaxants is a well-established practice in adults and children but not yet fully implemented in infants.

Several studies on more than 1,000 newborn infants demonstrated that premedication, both in term and preterm infants, facilitated procedures, reduced pain and stress and limited deterioration of vital parameters, such as heart rate, blood pressure, oxygen saturation and intracranial pressure (1-4). For the above reasons, premedication before endotracheal intubation is recommended in newborn infants

(1). Despite these recommendations, the optimal dosage and regimen have not yet been completely clarified and no validated scoring systems that can assess the level of sedation prior to endotracheal intubation have been published in the literature (5).

There are other reasons why neonatologists should control pain during respiratory assistance in newborn infants. Firstly, newborn infants are able to perceive pain. It has been extensively reported that neonatal infants have mature and functional ascending pain pathways capable of transmitting noxious impulses to the neocortex by 24 weeks of gestation and that immature descending pain pathways expose preterm infants and neonates to a greater intensity of pain for a prolonged period of time (6). Secondly, newborn infants receiving respiratory assistance are subjected to many painful procedures such as endotracheal suctioning, heel sticks, venipunctures and central line insertion. In addition, both mechanical ventilation and the underlying disease may induce pain. Adults studies have reported that prolonged mechanical ventilation caused them pain, anxiety, panic, nightmares or distress and trouble breathing (7). Prolonged pain has been shown to influence neonatal morbidity and have long-term adverse effects (8). However, there is still no consensus on the safety and efficacy of the drugs, especially opioids, used during neonatal mechanical ventilation (9). That is why our group decided to review the available evidence in the literature. This paper details pain control guidelines for clinicians performing mechanical ventilation, nasal continuous positive airway pressure (CPAP) and endotracheal intubation in term and preterm newborn infants, based on the available scientific evidence and knowledge. These guidelines are intended to provide an update on those published in 2009 (10), with the aim of promoting and disseminating good clinical practice as a standard of care to all neonatology services.

METHOD

Development of the guidelines

A panel of experts, comprising neonatologists and paediatric anaesthesiologists with proven experience in the field of analgesia and sedation who work within the pain study group of the Italian Society of Neonatology, received a mandate from Society to update these guidelines. They included professionals with known experience in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (11). The group, conducted a literature review from 1966 to month 2017 on each procedure by consulting Medline, the Cochrane Library, Scopus and the ISI Web of Knowledge databases, using both medical subject heading terms and freely chosen words in various combinations. These were: infant, newborn, neonates, pain, analgesia, stress, sedation, anaesthesia, premedication, mechanical ventilation, non-invasive ventilation, nasalCPAP and non-pharmacological intervention. Specific terms for the drugs involved were also used, including fentanyl, morphine, opioids, benzodiazepines and midazolam. No search restrictions were applied, such as language, to achieve the widest possible search coverage.

Each member of the working group took responsibility for one or more procedures, analysing the available literature and assessing each paper according to the GRADE approach (11). This first step towards the development of the guidelines was documented in an *ad hoc* format to summarise the quality of the evidence supporting the efficacy and safety of each analgesic intervention. These were as follows: high versus moderate, based on evidence from randomised controlled clinical trials and or systematic reviews of randomised trials and low or very low, based on case-control or observational studies. Paper were downgraded in order to consider the study limitations for randomised clinical trials, in accordance with the GRADE system, to take account of inconsistency, indirectness, imprecision or, publication bias. Papers were also upgraded to consider a large magnitude of effects, dose-response relationships and the presence of any plausible confounders the could be expected to reduce a demonstrated effect. The working group held monthly meetings over a period of six months and reached a consensus on the quality of the evidence and the final grade of recommendation -strong versus conditional -, for each pain control method.

The grades of the recommendations stated in this paper reflect the extent to which the positive effects expected from the use of a single analgesic method in the newborn infant outweigh the unwanted effects. Strong means that the desirable effect achieved by adhering to the recommendation unquestionably outweighs any undesirable effects and most patients would benefit from the recommended treatment. Conditional applies to methods that probably have more benefits than side effects but their value is less than certain. According to this classification, strong recommendations should be implemented as standard care, while conditional recommendations should be seen as therapeutic options to share with the healthcare team treating the infant, other caregivers and parents.

The expected effects, or outcomes, of the use of analgesics: less pain, when measured with a pain scale; better composite pain scores; better physiological and behavioural parameters in terms of decreases in heart rate, desaturations, vagal tone, facial expressions, crying times; other outcomes that indicate a reduced need for further treatments and additional costs to prevent the complications related to inadequate pain control.

Once approved by the working group, the document was submitted for critical review by a multidisciplinary external team of experts, including paediatricians, neonatologists, nurses, anaesthetists, psychologists, and a representative of the Italian Society of Neonatology's working group on quality of care to check for methodological issues. Representatives of parents' associations also reviewed and approved the document. The board of the Italian Society of Neonatology approved the final document and circulated it to all associate neonatologists.

RESULTS

Invasive mechanical ventilation

During mechanical ventilation, neonatal stress should be minimised by reducing and concentrating painful manoeuvres, reducing lighting and noise levels, providing appropriate containment for the newborn infant, individualising treatments, promoting the presence of parents in the neonatal intensive care unit and using non-pharmacological analgesia provided by sweet solutions (12). *Very*

low quality of evidence. Strong recommendation. Comfort manoeuvres are not able to reduce pain scores during endotracheal suction (12). *Very low quality of evidence. Conditional recommendation.*

The systemic analgesic pharmacological approach during invasive mechanical ventilation will differ according to whether mechanical ventilation is expected to last for a short or long time.

Short duration of mechanical ventilation expected, mainly in preterm infants affected by respiratory distress syndrome

To reduce acute pain in newborn infants on mechanical ventilation, intermittent boluses of opioids are recommended, as required, on the basis of pain scores and before invasive procedures. The aim of this individualised approach to pain is to administer the lowest effective dose of opioids and to reduce complications from uncontrolled pain, while reducing the risk of high cumulative doses of opioids (Appendix 1) (13-15). *Moderate quality of evidence. Strong recommendation*.

Clinicians should favour boluses of fentanyl (1-3 mcg/kg intravenous - over at least five minutes) or remifentanil (0.25 mcg/kg/minute) during painful manoeuvres, instead of morphine, if the patient is at risk of hypotension and or is less than 27 weeks of gestational age (16). *Moderate quality of evidence. Conditional recommendation.*

Boluses of morphine (10-50 mcg/kg, maximum 100 mcg/kg, over 15-30 minutes) should be provided instead of fentanyl if there is a risk of increased intra-abdominal pressure (17). *Low quality of evidence. Conditional recommendation.*

To implement this individualised approach of boluses as required in clinical practice, it should be mandatory to standardise pain monitoring in the neonatal intensive care unit, based on pain recorded as the fifth vital sign. Pain scores should be recorded in the medical record, together with the analgesic strategies used on the basis of pain scores, as well as the efficacy of the treatment.

Long duration of mechanical ventilation expected, in term and preterm newborn infants with severe respiratory failure

Clinicians should favour more constant analgesia, provided by continuous infusions of opioids, in term and preterm infants with severe respiratory failure due to surgical diseases, malformations, severe sepsis, pulmonary hypertension and neurological diseases, who might require frequent boluses of opioids to maintain adequate analgesia and sedation (18-20). *Moderate quality of evidence. Conditional recommendation*. However, these studies, mostly conducted on preterm infants with respiratory distress syndrome, failed to demonstrate that providing continuous infusions of opioids to infants on mechanical ventilation improved short-term neurological outcomes, severe intraventricular haemorrhage, periventricular leukomalacia or death within 28 days of life (18,20).

Algometric scores should always be used to titrate the dose of opioids. *Quality of evidence could not be evaluated. Strong recommendation*.

Patients should be given high initial doses in order to reach a rapid analgesic effect, then these should be decreased to the lowest effective dosage, based on pain scores. This approach reduces the cumulative dose of opioids and decreases the risk of tolerance (21,22) (Appendices 1 and 2). *Low quality of evidence. Conditional recommendation*.

Morphine infusions are not recommended in hypotensive preterm infants with a gestational age of less than 27 weeks (16). *Moderate quality of evidence. Strong recommendation.*

Clinicians should favour continuous infusions of fentanyl (loading dose 1-2 mcg/kg over 30 minutes, maintenance dose 0.5-3 mcg/kg/hour), instead of morphine, in the presence of one or more of the following conditions: risk of hypotension and or a gestational age of less than 27 weeks (16) and reduced gastrointestinal motility (23). *Moderate quality of evidence. Conditional recommendation.*

Fentanyl should also be preferred to morphine in the presence of renal failure, as it is completely inactivated by the liver. *Quality of evidence could not be evaluated. Conditional recommendation.*

Continuous infusions of morphine should be favoured (loading dose 25-50 mcg/kg, maximum 100 mcg/kg over one hour, maintenance dose 7-50 mcg/kg/hour) in newborn infants who have undergone abdominal surgery and have a risk of increased intra-abdominal pressure (17). *Low quality of evidence. Conditional recommendation*

Additional boluses of opioids should be administered before painful invasive or skin breaking procedures, if continuous infusion or non-pharmacological analgesia are inadequate. In cases where long-term treatments are required, when the existing opioid can no longer effectively control the pain, even at the maximum recommended dose, then rotate the opioids (21). *Very low quality of evidence. Conditional recommendation.*

Strategies to prevent and manage problems due to prolonged treatment with opioids during mechanical ventilation (for more comprehensive information on signs and symptoms associated with prolonged treatment with opioids during mechanical ventilation see Appendix 2).

A number of strategies are available to reduce the incidence of tolerance. These include tailoring opioids on the basis of pain intensity by giving initial high dosages in order to reach a rapid analgesic effect then decreasing the dosages on the basis of pain scores. Clinicians can also use short-acting opioids for procedural pain and long-acting opioids for more prolonged pain. Moreover, we recommend that after about four days of fentanyl infusion, and after about 14 days of morphine infusion, even before if the dose was greater than 40 mcg/kg/hour, clinicians should consider escalating the dose on the basis of pain scores. We also suggest combining opioids with N-methyl-D-aspartate receptor antagonists, such as intravenous ketamine at 0.25-0.5 mg/kg, although repeated ketamine usage may be neurotoxic to immature brains in the absence of noxious stimuli and its use is

often restricted to anaesthetists in some states (21,22,24). *Very low quality of evidence. Conditional recommendation.*

Different strategies can also be used to prevent and recognise the neonatal drug withdrawal. For example, use a consistent protocol to wean opioids. If the treatment with fentanyl or morphine has lasted less than five days, it is possible to decrease the original dose by 30-50% to start with, then by 20-30% every 6-8 hours. If the treatment with these two drugs has lasted for more than four days, especially if a continuous infusion has been used, decrease the original dose by 20% in the first 24 hours and then by 10% every 12 hours (25). *Very low quality of evidence. Conditional recommendation.*

The rate and duration of the tapering should be adjusted according to the patient's response and by using the Finnegan score (26) every four hours, to monitor the weaning. If the Finnegan score is less than eight, make sure that all environmental stressful stimuli have been reduced such as light, noise, handling. If the Finnegan score remains above eight, reverse the tapering, slow it down or pause it, for example by giving the patients 10% of the dose in 24 hours, while monitoring and managing the withdrawal symptoms. *Quality of evidence could not be evaluated. Conditional recommendation.*

Alternative therapeutic strategies can also be used, especially when the infusion needs to be discontinued. For example clinicians can administer morphine using an oral suspension of 0.1 mg/kg every six hours. This dosage has been used in babies born to opioids abusing mothers and should be tailored according to the pain response and withdrawal symptoms (27). *Low quality of evidence. Conditional recommendation;*

Clinicians can also give methadone as an oral suspension at an initial dose of 25-100 mcg/kg every six hours. Alternatively, equi-analgesic doses can be used calculated according to the scheme reported in Table 1. Methadone should be tapered in six or 11 days depending on the duration of treatment: 7-14 days or less than 14 days, respectively (28). *Very low quality of evidence. Conditional recommendation.*

Clinicians should suspect hyperalgesia when a dosage increase is followed by an increase in pain intensity. The following strategies should be used to manage hyperalgesia: reduce the dose of the current opioid; switch to longer-acting opioids such as morphine instead of fentanyl and methadone instead of morphine; use associated α2-adrenergic receptor agonists such as clonidine or dexmedetomidine, which can also be used to treat opioid withdrawal in neonates, and use associated N-methyl-D-aspartate antagonist drugs, such as ketamine at 0.1-0.25 mg/kg/hour. These drugs should be prescribed in line with the safety considerations described in the text tolerance earlier in this paper (21,29,30). *Low quality of evidence. Conditional recommendation.*

Sedation during mechanical ventilation

In some cases a more pronounced sedative effect is required in late-preterm and in term infants without hypotension, for example in cases of pulmonary hypertension, severe air leak or after major surgery. We recommend short acting benzodiazepines, such as midazolam (bolus 0.05-0.2 mg/kg intravenously over 15 minutes or continuous infusion 0.015-0.060 mg/kg/hour), in association with opioids. The association of benzodiazepines and opioids can help to reduce the dose of opioids or of muscle relaxants. This approach, used in clinical practice by the authors of the present guidelines, has not been documented in the literature. *Quality of evidence could not be evaluated. Conditional recommendation.*

Doses of midazolam should be individualised on the basis of post-conceptional age and the treatment should be limited to a few days. Clearance of midazolam is reduced by concomitant treatment with opioids and that is why midazolam should be used at lower dosages in mechanically ventilated newborn infants who are concomitantly treated with opioids. It is important to note that midazolam should be used with extreme caution in infants receiving fluconazole or erythromycin, as these drugs are metabolised by the same liver cytochrome enzymes (31).

Midazolam infusions are not currently recommended for preterm infants because of the increased incidence of adverse neurological events (32,33). *Low quality of evidence. Conditional recommendation.*

There is little clinical evidence to support the use of other drugs, such as dexmedetomidine.
A study evaluated the use of dexmedetomidine, a highly selective alpha-2 agonist receptor with sedative and analgesic effects, in 42 mechanically ventilated infants with a gestational age of 28-44 weeks. Using a dosage of 0.05-0.2 mcg/kg/hour for a total of 6-24 hours resulted in a good sedative effect and a good tolerance without significant adverse effects (34). The use of this drug has been approved by The Italian Agency for Drugs in 2016 for neonates where other analgosedative treatments have proved to be ineffective. However, due to limited available data, a judicious use is recommended. *Low quality of evidence. Conditional recommendation.*

Non-invasive ventilation with positive end expiratory pressure

There are no randomised clinical trials available that cover non-invasive ventilation with positive end expiratory pressure provided by nasal intermittent ventilation or CPAP.

Our recommendation is to minimise stress and use non-pharmacological analgesic techniques (12). *Very low quality of evidence. Conditional recommendation.*

Clinicians are advised to use intravenous boluses of opioids before major invasive procedures, at the minimum recommended dose (morphine 10-30 mcg/kg and fentanyl 0.5-1 mcg/kg) if infants have a gestational age of less than 27 weeks. A study that evaluated boluses of morphine in preterm infants on nasalCPAP showed reduced pain scores. However, a higher incidence of apnoea was detected in infants with a gestational age of less than 28 weeks and in those treated with dosages of morphine that were higher than 30 mcg/kg (35). *Low quality of evidence. Conditional recommendation.*

It is not necessary to discontinue opioids in newborn infants extubated with non-invasive ventilation, because the respiratory depression effect of the opioids usually resolve as tolerance develops. When transitioning from invasive to non-invasive ventilation, taper opioids slowly and monitor pain by using algometric scales. *Quality of evidence could not be evaluated. Conditional recommendation.* Clinicians should consider sedation with midazolam, as boluses or continuous infusion, in term babies with pneumothorax and, or, pneumonia. *Quality of evidence could not be evaluated. Conditional recommendation.*

Analgesia for respiratory assistance during therapeutic hypothermia

There is a complex interaction between asphyxia, hypothermia and analgesic drugs, as asphyxia may reduce renal and hepatic function, thus affecting drug metabolism. The function of the P450 complex, which metabolises many of the drugs used for analgesia and sedation, namely opioids and midazolam, is temperature-dependent. Mild or moderate hypothermia decreases the systemic clearance of cytochrome P450 metabolised drugs by between 7% and 22% per degree of Celsius below 37°C during cooling (36). Clinicians should be aware of the altered pharmacokinetics and pharmacodynamics of sedative and analgesic drugs during hypothermia and of the need for careful dose titration (37).

There are no studies about the best opioid or the most appropriate regimen, namely repeated boluses or continuous infusion, to be used during respiratory assistance in cooled infants. Clinicians using fentanyl as their first choice can administer a loading dose of 1-2 mcg/kg over one hour and then titrate the infusion to 0.5-1 mcg/kg/hour based on the infant's response. Plasma fentanyl concentrations can increase at the end of the cooling period and remain elevated in the first hours after rewarming, so monitoring of fentanyl side effects should continue after fentanyl is discontinued (37). Clinicians using morphine as their first choice should not exceed 10 mcg/kg/hour, as serum morphine concentrations in the toxic range have been reported to be more common above this infusion rate (38). *Very low quality of evidence. Conditional recommendation.*

Intravenous boluses of opioids (0.5-1 mcg/kg of fentanyl and 10-50 mcg/kg of morphine) instead of continuous infusion can help to reduce the risk of high cumulative doses of opioids, while controlling dangerous pain and agitation due to hypothermia. See paragraph on short expected duration of mechanical ventilation. *Quality of evidence could not be evaluated. Conditional recommendation.*

Endotracheal intubation

Premedication for non-emergent intubation in newborn infants is strongly recommended, to ensure a more rapid, less painful and less traumatic and safer manoeuvre (1-4). *Moderate quality of evidence. Strong recommendation.* For a more comprehensive literature review on endotracheal intubation see Appendix 3.

Clinicians are advised to use the following sequence. The patient should be given the following intravenously: atropine (0.01-0.02 mg/kg) plus fentanyl (2 mcg/kg over at least five minutes) plus succinylcholine (suxamethonium) (2 mg/kg) or rocuronium (0.5-1 mg/kg) immediately prior to intubation (39-42). *Moderate quality of evidence. Conditional recommendation.* Muscle relaxant can be avoided in newborn infants that are not vigorous, for example those with an extremely low birth weight, those that are severely asphyxiated and those affected by muscular disorders.

Alternative options and the procedures for special cases are as follows. Haemodynamically stable infants with a post-conceptional age of less than 32 weeks should be given the following intravenously: atropine (0.01-0.02 mg/kg) plus fentanyl (2 mcg/kg over at least five minutes) plus midazolam (0.1 mg/kg) (4,43,44). *Low quality of evidence. Conditional recommendation.*

Haemodynamically stable infants, with a postnatal age greater than 24 hours should be given the following intravenously, with the dose tailored to the patient's response: atropine (0.01-0.02 mg/kg) plus propofol (1-2.5 mg/kg) (45-47). *Low quality of evidence. Conditional recommendation.*

In haemodynamically unstable infants, with the exception of the extreme preterm infant: atropine (0.01-0.02 mg/kg intravenously) plus ketamine (1-2 mg/kg intravenously) (3). *Low quality of evidence, conditional recommendation.*

Before the INtubation-SURfactant-Extubation (INSURE) procedure, when a more rapid recovery of the respiratory activity is required, use Atropine 0.01-0.02 mg/kg followed by drugs with a short half-life, such as remifentanil 2 mcg/kg over 60 seconds and succinylcholine 2 mg/kg; alternatively, atropine can be followed by a drug without a significant depressive effect on the respiratory function, such as propofol 1-2.5 mg/kg. The time needed to recover spontaneous respiratory activity after the administration of sedative analgesic and muscle relaxant drugs is very variable and unpredictable and respiratory autonomy should be carefully assessed before extubation. It can be necessary to provide respiratory support to the newborn infant until the resumption of adequate spontaneous respiratory activity. Alternatively, and whenever possible, clinicians can use an antagonist drug, such as naloxone to reverse the effect of opioids, flumazenil to reverse the effect of benzodiazepines and sugammadex to reverse the effect of rocuronium. There is currently no literature on the use of sugammadex in newborn infants and it is important to remember that reversal agents often have a shorter half life than the opioids they are reversing (2,39,42,45,46,48,49). *Moderate quality of evidence. Conditional recommendation.*

If a venous line is not available, despite every effort having been made to establish an intravenous line, especially in the delivery room, consider using a maximum of two doses of intranasal midazolam (0.2 mg/kg) (50). *Low quality of evidence. Conditional recommendation.*
The safety considerations for remifentanil, ketamine, propofol and succinylcholine are reported in Table 2.

DISCUSSION

This paper reports the recommendations from a panel of experts after they used the GRADE system to review the quality of the literature on pain and stress control in newborn infants undergoing endotracheal intubation and assisted ventilation. The Society wanted to carry out this review as they hoped that the resulting recommendations would promote and disseminate good clinical practice.

This review shows that, despite the fact that many studies are available, the quality of the evidence supporting the efficacy and safety of each analgesic intervention was often low or moderate. The reasons for this included the relatively low number of patients and their characteristics, for example heterogeneous gestational and postnatal ages, and the heterogeneous drug dosages and the variable presence of concomitant drugs.

Overall, there is still a gap in knowledge, which includes, but is not limited to, the definition of the exact dose and therapeutic regimen of analgesic drugs able to counteract the adverse effects of pain and stress, without significant side effects. For this reason, strong recommendations cannot be universally given.

Despite this, we thought that it was important to raise awareness on the subject. Our working group felt that evidence-based tools should be shared so that reasoned and informed choices could be made about different therapeutic options by the whole team of healthcare providers, other involved caregivers and parents.

Throughout the evaluation process the academic panel felt the strong need to advocate for a practical guideline that protects the developing neonate from pain, but also sensitises the healthcare providers to the notion of stress and pain endured by their patients.

The review produced five strong recommendations on standards of care. One, reduce neonatal stress and use non-pharmacological analgesia during invasive ventilation. Two, favour intermittent boluses of opioids, administered after pain scores and before invasive procedures, during short expected periods of mechanical ventilation, mainly in preterm infants affected by respiratory distress syndrome. Three, do not use morphine infusion in preterm infants under 27 gestational weeks. Four, always use algometric scores to titrate analgesic drugs doses. Five, use premedication before endotracheal intubation for a more rapid, less painful, less traumatic and safer manoeuvre.

We also developed 30 conditional recommendations on therapeutic options, including the infusion of opioids during prolonged ventilation, instead of boluses as required. Indeed, while it may seem intuitive that lower levels of opioids are better, the negative sequelae from undertreated pain may be even more harmful than the incompletely known consequences of opioids.

CONCLUSION

Our review produced 35 recommendations on standard care and therapeutic options relating to the analgesia and sedation of newborn infants during ventilation and before endotracheal intubation. Further prospective randomised clinical trials are urgently needed in order to broaden our knowledge about benefits and hazards of analgesic drugs in the fragile population of newborn infants admitted to neonatal intensive care unit.

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CONFLICTS OF INTEREST

The authors have no conflict of interests to declare.

ABBREVIATIONS:

CPAP, continuous positive airways pressure; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

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Appendix 1. Relevant notes when using opioids

Dosages: These must be calibrated on the basis of birth weight, gestational age at birth and postnatal age, administering the lower doses to infants with lower birth weights, gestational ages and postnatal ages.

Boluses: These should be always administered before painful procedures (central venous line insertion, chest drains etc) and in the presence of prolonged pain (such as an Échelle Douleur Inconfort Nouveau-Né – EDIN - score > 6).They can be repeated every two hours (fentanyl) or every four hours (morphine). Remifentanil, has a half-life of about 10 minutes (51,52), can be repeated after 15-30 minutes if necessary. Boluses should be administered slowly.

Continuous infusion: After discontinuation of the fentanyl infusion, continue to monitor symptoms. Fentanyl can redistribute from the deep tissues, such as adipose and muscle tissue where it accumulates because it is highly lipophilic, to the blood.

Side effects: Correlate to the cumulative dose of opioids. Include longer duration of mechanical ventilation, delayed attainment of full enteral feeding, hypotension (morphine) and negative effect on development (15,16,18,23,53-55). Scores on the intelligence quotient subtest of visual analysis, obtained in children at five years of age, indicated a significant negative correlation to morphine consumption during the neonatal period (54), although this effect was not confirmed at 8-9 years of age (55). Another study demonstrated that a continuous infusion of fentanyl in very preterm infants, given at 1 mcg/kg/hour during mechanical ventilation, was associated with a significant decrease in eye and hand co-ordination skills when they were evaluated at two years of corrected age (53).

Appendix 2. Signs and symptoms associated with prolonged treatment with opioids during mechanical ventilation (21,22)

Tolerance: This is a reduced pharmacological efficacy and it rarely occurs when treatment lasts less than 96 hours. Be aware that the reduced efficacy of ongoing treatment with opioids can be due to hyperalgesia or to the worsening of pain as well as to the development of tolerance. Moreover, neonates may seem to be developing tolerance when there are in fact other sources of pain or discomfort, such as worsening respiratory status or ventilator malfunction.

Drug withdrawal: This can occur when there is an abrupt reduction or discontinuation of opioids. It includes a group of symptoms that mimics neonatal abstinence syndrome, accompanied by jitteriness, generalised tremours, convulsions, sweating, fever, mottling, excessive sucking or rooting, poor feeding, vomiting, diarrhoea and needs to be evaluated with the help of the Finnegan score (26).

The development of tolerance and of drug withdrawal depends on various factors. These include the type of administered opioid: tolerance and drug withdrawal occur more frequently during treatments with synthetic opioids and short acting opioids, such as fentanyl and remifentanil, than natural opioids such as morphine. It is more common in males, preterm infants, with a longer duration of therapy, when there are simultaneous infusion of sedatives like midazolam. It is also more common if there is a lower initial dosage of opioids. Tolerance and drug withdrawal are less frequent when opioids are used to reduce postoperative pain compared to other indications.

Hyperalgaesia: This term refers to pain exacerbated by opioid treatment. It is due to the hypersensitisation of afferent neurons, the increased production and release of excitatory neurotransmitters activating N-methyl-D-aspartate receptors and the decreased reuptake of excitatory neurotransmitters. It can even occur in the absence of tolerance syndrome.

Appendix 3. Further work on the subject of analgesia and sedation before endotracheal intubation

Premedication before endotracheal intubation can have different goals: to reduce and pain, facilitate procedures and reduce the side effects due procedures.

In order **to reduce pain and stress** around endotracheal intubation, remifentanil, a short-acting opioid, has been successfully used at an intravenous dosage of 2 mcg/kg over two minutes (2). Unfortunately, very little research is available on remifentanil in newborn infants and concerns have been raised about its safety (Table 2) (2,43,48,49,56,57). Also, the combined use of intravenous midazolam (0.05-0.20 mg/kg) and intravenous morphine (150 mcg/kg) or fentanyl (1-2 mcg/kg) has been shown effective. In contrast, just fentanyl, even at an intravenous dosage of 2 mcg/kg may not ensure enough control of pain and stress (4,43). Morphine is not the drug of choice for this specific procedure, since it has only been shown to be efficacious at high dosages and its onset of action is delayed compared with fentanyl, by at least 5-10 minutes from the end of the infusion. Moreover, it has been demonstrated that morphine causes amplitude-integrated electroencephalography (aEEG) depression in the six hours following endotracheal intubation (58).

Ketamine at an intravenous dosage of 1-2 mg/kg has also been shown to be effective in reducing pain and stress due to intubation in newborn infants (3). However, very little research is available on this drug in newborn infants and the short-term and long-term side effects, especially in very preterm infants, are little known (Table 2) (3,59).

One study showed that nasal midazolam provided rapid and effective sedation to intubated neonates in the delivery room (44). Another study showed a lower efficacy of nasal ketamine (2 mg/kg) compared to nasal midazolam (0.2 mg/kg), but similar side effects, in preterm neonates requiring non-emergency endotracheal intubation for surfactant instillation in the delivery room (50). There is no available data at the moment on any other drug used for pain control during endotracheal intubation in infants.

The following strategies have been shown effective **to facilitate endotracheal intubation** and thus reduce the time needed for intubation, limit the number of attempts and avoid local trauma due to laryngoscopy:

- Intravenous fentanyl (2-5 mcg/kg), combined with a muscle relaxant (succinylcholine 2 mg/kg or rocuronium 0.5-1 mg/kg) (39-42);
- Intravenous remifentanil (2 mcg/kg administered over two minutes) has been shown to improve overall intubation conditions (2,48). However, intravenous remifentanil (1 mcg/kg) is less effective than an association of morphine and midazolam after the first attempted intubation, due its short half-life (56). Moreover, monotherapy with remifentanil, even at 3 mcg/kg, showed less efficacy when compared with fentanyl 2 mcg/kg plus succinylcholine (49). Remifentanil 1-2 mcg/kg, intravenously as a fast bolus and followed by an intravenous saline flush in 30 seconds provided insufficient sedation and was associated with a high risk of chest wall rigidity in preterm neonates (57). Remifentanil 1 mcg/kg plus midazolam improved overall intubation conditions compared with morphine 150 mcg/kg plus midazolam (43). In conclusion, concerns persist over remifentanil monotherapy at high doses (2-3 mcg/kg), especially for safety reasons. The association with a muscle relaxant may be favourable (Table 2);
- Intravenous propofol (1-2.5 mg/kg). It should be remembered that propofol may cause hypotension with a *nadir* 10-20 minutes following administration, especially at lower gestational ages and during the first 24 hours of life (Table 2). Therefore, propofol should be only used in patients with normal blood pressure, after the first 24 hours of life. Blood pressure should be carefully monitored for at least 30 minutes after propofol administration (45-47).
- Midazolam (0.2 mg/kg) given in each nostril, if intravenous access is not available, has been shown to be more efficient than nasal ketamine (2 mg/kg) with regard to adequately sedating neonates requiring intubation in the delivery room (50).

When it comes to **reducing the complications related to endotracheal intubation** - namely increased intracranial pressure, bradycardia, desaturation and glycaemic stress - studies from the literature have showed that anaesthesia, appropriate sedation and muscle relaxants, combined with opioids, are able to prevent increases in blood and intracranial pressure, desaturations and glycaemic stress. Atropine is useful for reducing bradycardias (4).

Table 1. Equivalent doses of the main opioids in children.

Agent	**Dose (mcg/kg)**
Morphine	10-100
Fentanyl	1-3
Methadone	25-100

It appears from the table that fentanyl is about 25 times more powerful than methadone. Therefore, to calculate the bolus dose of methadone to be administered in an infant receiving continuous infusion with fentanyl it is necessary to multiply by 25 the dose of fentanyl administered over 1 hour; i.e. fentanyl 2 mcg/kg/h, corresponds to methadone 50 mcg/kg/dose to be given every 6 hours.

Methadone should then be tapered in 6 or 11 days depending on the duration of treatment (7-14 days or > 14 days, respectively) (56). *Very low quality of evidence, conditional recommendation.*

Table 2. Safety considerations on drugs for analgosedation before endotracheal intubation in newborns.

Drug	**Warnings**
Remifentanil	6 studies on 115 newborns (2,43,48,49,56,57) using 1-3 mcg/kg, reported a high incidence of chest wall rigidity (about 10%, but up to 43% if infused over 30 seconds) and laryngospasm, especially among the most immature infants. These side effects are preventable by slow infusion; alternatively, they can be antagonized by the use of muscle-relaxants or naloxone.
Ketamine	Not yet been extensively studied in the newborn; it did not show any significant cardiovascular effects in newborns, including preterm infants, when used during invasive procedures (3,59). Its use is restricted to anesthesiologists in some states.

Propofol	2 studies that used propofol as premedication for neonatal endotracheal intubation (75 newborns ranging from 24 to 40 weeks GA), at doses ranging from 1 to 6 mg/kg, reported the risk of significant arterial hypotension (up to 39% of cases) especially during the first postnatal day. Lower blood pressure values were observed 10-15 minutes after drug administration (46,47). Its use is restricted to anesthesiologists in some states.
Succinylcholine	Can cause malignant hyperthermia in predisposed subjects, especially in association with anesthetic gases. As a depolarizing agent, it can increase potassium levels. There have been rare reports of cardiac arrest with elevated potassium levels in patients with other underlying diseases, such as congenital cerebral palsy, tetanus, Duchenne muscular dystrophy, close head injury and in children with undiagnosed muscle disorders. It can also increase intracranial and intraocular pressure (60).