Stimulating and maintaining spontaneous breathing of preterm infants at birth

Dekker, J.

CHAPTER 9

Sedation during minimal invasive surfactant therapy: a randomized controlled trial

J Dekker
E Lopriore
HA van Zanten
RNGB Tan
SB Hooper
AB te Pas

Arch Dis Child Fetal Neonatal Ed 2018;0:F1-F6

ABSTRACT

AIM

Although sedation for endotracheal intubation of infants is widely adopted, there is no consensus whether sedation should be used for minimal invasive surfactant therapy (MIST). We compared, in a randomized controlled setting, the level of stress and comfort of preterm infants during MIST with and without receiving low dose sedation.

METHODS

Infants between 26 - 36 weeks gestational age were randomized to receive either low dose sedation (1 mg/kg propofol iv) or no premedication during MIST procedure. Standard comfort care was given in both groups, which consisted of administering sucrose in the cheek pouch of the infant and containment. Primary endpoint was the percentage of infants assessed to be comfortable during the procedure (COMFORTneo score < 14). Secondary parameters included complications of both the MIST procedure and low dose sedation administration.

RESULTS

In total 78 infants were randomized and analyzed, with a median (IQR) gestational age of 29^{+0} (28^{+0} – 32^{+0}) weeks. The percentage of infants with a COMFORTneo score < 14 during MIST was significantly higher in the sedated group (32/42 (76 %) vs 8/36 (22 %), p<0.001). The incidence of desaturation (SpO_2 < 85 %) during the procedure was significantly higher in the sedated group (38/42 (91 %) vs 25/36 (69 %), p=0.023), and infants needed more often nasal intermittent mandatory ventilation during the procedure (39/42 (93 %) vs 17/36 (47 %), p<0.001). There were no differences in incidence of hypotension, bradycardia, intubation or pneumothoraxes.

CONCLUSION

Low dose sedation increased comfort during MIST procedure in preterm infants, but the need for transient non-invasive ventilation was increased.

INTRODUCTION AND RATIONALE

Many preterm infants have respiratory distress syndrome due to surfactant deficiency.(1) Although nasal continuous positive airway pressure (CPAP) is effective as the initial means of respiratory support in most premature infants, a proportion of infants require surfactant therapy in order to succeed on CPAP.(2, 3) However, this has traditionally involved intubation followed by mechanical ventilation. Avoiding mechanical ventilation has the potential to decrease the risk for intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD) and death.(4, 5) This can be achieved with MIST, where surfactant is administered to a spontaneously breathing infant who then remains on CPAP.(6, 7) The most common method for this approach involves visualising the vocal cords with a laryngoscope and catheterising the trachea using a semi-rigid catheter, after which the surfactant is instilled.(8) Currently, many Neonatal Intensive Care Unit (NICU) centers, including in the Netherlands, have adopted this procedure.

There is general consensus that an infant should be adequately sedated when an endotracheal intubation procedure is performed.(9-12) Although it is known that visualising the vocal cords with a laryngoscope is highly uncomfortable(13), there is still no consensus on whether or not to use sedation during MIST, particularly when a laryngoscope is used. The use of a laryngoscope can lead to cardiovascular responses and attempts to resist the laryngoscope might result in an increased risk of intraventricular hemorrhage by impairing cerebral venous return.(14-17) While sedation might also increase the chance for an uneventful, smooth and successful procedure, sedation might compromise the infant's respiratory drive which is a prerequisite for MIST. Reported experience from feasibility studies suggests that the MIST procedure is generally well tolerated without any premedication.(1, 6, 8) However, Klotz et al.(18) reported in a European survey that almost half of the neonatologists use premedication during MIST procedures, including sedatives.

We have performed a randomized controlled trial where we hypothesized that low dose sedation would increase the comfort of preterm infants during the MIST procedure with minimal side-effects. The aim of this study was to compare the level of comfort of preterm infants receiving low dose sedation versus no sedation during MIST procedure.

METHODS

A randomized controlled trial was conducted at the Leiden University Medical Center, including all preterm infants with a gestational age between 26 - 37 weeks needing surfactant therapy for respiratory distress syndrome according to the local criteria (FiO_2 > 0.3 and PEEP ≥ 8 cm H_2O). Opaque sealed envelopes were used to determine randomization: low dose sedation or no premedication. We excluded infants who had an imminent need for intubation because of respiratory insufficiency, expressed by apnea and/or persistent acidosis. Infants with a pneumothorax or pulmonary hemorrhage were also excluded. All infants < 30 weeks gestational age (GA) received caffeine in the delivery room or at admission to the NICU. Infants > 30 weeks GA received caffeine in case of recurrent apnea. Allocation was stratified by GA (26^{+0} – 31^{+6} and 32^{+0} – 36^{+6} weeks) using variable block sizes (4-8).

The intervention consisted of the use of administering intravenous propofol (1 mg/kg) for sedation during the MIST procedure. This is a reduced dose compared to the standard dose of 2.5 mg/kg used for neonatal intubation, to prevent side effects as respiratory depression. Propofol was administered intravenously, either by peripheral or central vein dependent on the iv access point of the infant. The administration was performed slowly directly before MIST, to refrain from thoracic rigidity and pain at administration point. Both groups received standard comfort care, which consisted of administering sucrose 24% in the cheek pouch of the infant and containing the infant during the MIST by swaddling the infant or gently placing the hands of a caregiver on the infant's body.

The main study parameter was the COMFORTneo score; the primary endpoint was the percentage of infants with a COMFORTneo score < 14 during the procedure. The COMFORTneo score is a validated instrument for measuring objectively the (dis) comfort of a preterm infant,(19) and is used by trained NICU nurses as standard of care to assess the comfort of a preterm infant every shift at the NICU of the LUMC. The procedure was video recorded, where both the face of the infant and the motions of one of the extremities could be observed, while the other extremities were contained. The recordings were coded and edited so that the administration of sedation was not visible, and two independent NICU nurses, blinded for the allocation, reviewed the recordings and measured the level of comfort using the COMFORTneo scale. Both nurses assessed comfort in 10 MIST procedures, after which interrater reliability between these nurses was assessed. Cohen's κ was used to assess interrater reliability, where 0 means no agreement and 1 means total agreement. A Cohen's κ > 0.4 was considered reasonable. When interrater reliability appeared to be < 0.4, an additional NICU nurse

assessed the same 10 MIST procedures, to find reasonable reliability between two NICU nurses. When reasonable Cohen's κ was achieved within two NICU nurses, the remaining MIST procedures were subdivided into those two nurses for assessment.

Secondary study parameters were: the occurrence of nasal intermittent mandatory ventilation (nIMV) during and immediately after the procedure, intubation need during the procedure and within 24 hours, number of attempts of insertion of the angio-catheter, duration of the procedure, complications occurring during the procedure (desaturation < 85 %, hypotension with mean < GA, bradycardia < 80 bpm, nasal hemorrhage), other complications (pneumothorax, pulmonary hemorrhage, resuscitation, intraventricular hemorrhage ≥ grade 3, death), and heart rate and blood pressure before, during and after the procedure. Oxygenation and heart rate were measured with the Masimo SET pulse oximeter. Arterial blood pressure was measured using an IntelliVue MP30 Philips Monitor. If an arterial line was not present, blood pressure was measured non-invasively using an appropriately sized neonatal cuff (Philips). All clinical parameters were stored every minute in the local Patient Data Management System (Metavision, IMDSoft, Tel Aviv, Israel).

As there was no data available on comfort during MIST to base the sample size on, we based our sample size calculation on a study that compared intubation during sevoflurane anaesthesia with awake intubation in preterm infants.(20) In this trial, the incidence of hypertension, which is a sign of discomfort, was 25% in the anaesthetized infants as compared to 56% in awake infants. To detect a comparable decrease in the incidence of COMFORTneo score > 14 when using propofol, with a power of 80% and an α error of 5% (two-tailed test), we required 39 infants for each arm.

The ethical committee of the LUMC approved the study protocol. Informed parental consent was obtained if time permitted to do so before MIST. However, when MIST was imminent and there was no time to approach parents for consent or this was considered inappropriate, deferred consent was asked at a more appropriate time after the procedure. This study was registered in www.trialregister.nl, with registration number NTR5010.

Statistical analysis was performed with SPSS software version 23.0 (SPSS, Chicago, Illinois). Demographics of the sedated and the non-sedated group were compared by α^2 test, Student's t-test and Mann-Whitney U test based on normality of the data. Linear study parameters that were assessed once per infant were compared by a two-way factorial ANOVA or a linear mixed-effect regression model in multiple assessments,

including both the randomization and stratification group. Categorical outcomes were assessed by Fisher's exact test. Two-sided p-values <0.05 were considered statistically significant.

RESULTS

A total of 110 eligible infants were admitted to the NICU between January 2015 and July 2017, of which 22 infants were not randomized (Figure 1). However, 4 infants in the sedated group and 6 infants in the non-sedated group were excluded from analysis. A total of 78 infants were analyzed, of which 42 in the sedated group and 36 in the non-sedated group. There were no differences between the groups in GA, birth weight or gender (Table 1).

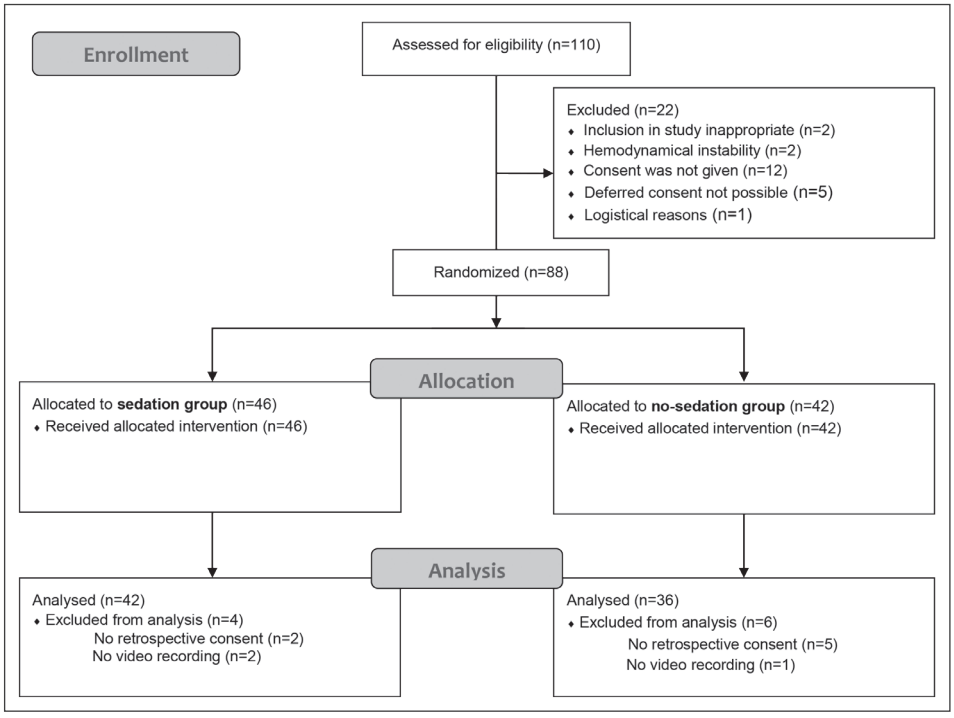

Figure 1 | CONSORT flow diagram

Table 1 | Demographical data

	Sedation group n = 42	No sedation group n = 36	*p*-value
Gestational age[a]	29^{+0} (27^{+5} – 32^{+0})	29^{+0} (28^{+0} – 31^{+0})	0.731
Birth weight (grams)[b]	1475 ± 575	1502 ± 606	0.837
Gender (% males)[c]	26/42 (62%)	20/36 (56%)	0.647

Data are presented as median (IQR) for non-parametric data ([a]), mean ± SD for parametric data ([b]) and n (%) for categorical data ([c]).

MIST procedure

Time point after birth when MIST procedure was performed was not different (sedated vs non-sedated group: median (IQR) 5.5 (3 – 15) hours vs 6.5 (3 – 14) hours, p=0.7). The number of attempts needed to insert the angio-catheter in the trachea was not different (1 (1 – 2) attempts vs 1 (1 – 2) attempts, p=0.982). There was no difference in total duration of the MIST procedure (246.1 ± 174.8 s vs 246.1 ± 178.4 s, p=0.641).

COMFORTneo score

The percentage of infants with a COMFORTneo score < 14 during MIST was significantly higher in the sedated group when compared to the non-sedated group (32/42 (76%) vs 8/36 (22%), p<0.001).

The mean ± SD COMFORTneo score during MIST was significantly lower in the sedated group compared with the non-sedated group (12 ± 3 vs 17 ± 4, p<0.001).

Complications

The incidence of desaturation was significantly higher in the sedated group (38/42 (91%) vs 25/36 (69%), p=0.023). There was no difference in mean blood pressure in the 30 minutes before MIST, during MIST and 30 minutes after MIST (Table 2). The incidence of hypotension was not significantly different between the groups (p=0.282), as was volume expansion as treatment of hypotension (p=1.000) (Table 2). In both groups, heart rate was significantly lower during and after the procedure when compared to before the MIST procedure. In the sedated group, the difference in heart rate was significantly greater between the periods before, during and after MIST when compared to the non-sedated group (p=0.002). There was no difference in the occurrence of bradycardia (heart rate < 100 bpm, p=0.556) (Table 2).

More infants in the sedated group needed nIMV during MIST (39/42 (93%) vs 17/36 (47%), p<0.001), but there was no difference in duration of nIMV given (median (IQR) time 7 (3 – 21) minutes vs 6 (3 – 12) minutes, p=0.274). Applying nIMV was not influenced by the different GA strata (Figure 2).

Table 2 | Demographical data

	Sedation group n = 42	No sedation group n = 36	*p*-value
Incidence of desaturation[a]	38/42 (91%)	25/36 (69%)	0.023
Incidence of hypotension[a]	9/30 (30%)	2/17 (12%)	0.282
Treatment for hypotension[a]	3/9 (33%)	0/2 (0%)	1.000
Blood pressure (mean mmHg)[b]			0.145
Before MIST	37 ± 8	38 ± 7	
During MIST	35 ± 7	39 ± 5	
After MIST	35 ± 7	38 ± 4	
Incidence of bradycardia[a]	9/42 (21%)	5/35 (14%)	0.556
Heart rate (beats per minute)[b]			0.002
Before MIST	151 ± 16	148 ± 13	
During MIST	143 ± 14	147 ± 13	
After MIST	141 ± 13	146 ± 14	
Need for nIMV[a]	39/42 (93%)	17/36 (47%)	< 0.001
Duration of needed nIMV (minutes)[c]	7 (3 – 21)	6 (3 – 12)	0.274
Intubation during MIST[a]	1/42 (2%)	4/36 (11%)	0.175
Intubation < 24 h after MIST[a]	10/42 (24%)	6/36 (17%)	0.576
Incidence of pneumothorax[a]	3/42 (7%)	1/36 (3%)	0.620
Incidence of pulmonary hemorrhage[a]	1/42 (2%)	0/36 (0%)	1.000
Intraventricular hemorrhage ≥ grade III[a]	2/42 (5%)	0/36 (0%)	0.497
Death[a]	1/42 (2%)	1/36 (3%)	1.000

Data are presented as n (%) for categorical data ([a]), mean ± SD for parametric data ([b]) and median (IQR) for non-parametric data ([c]).

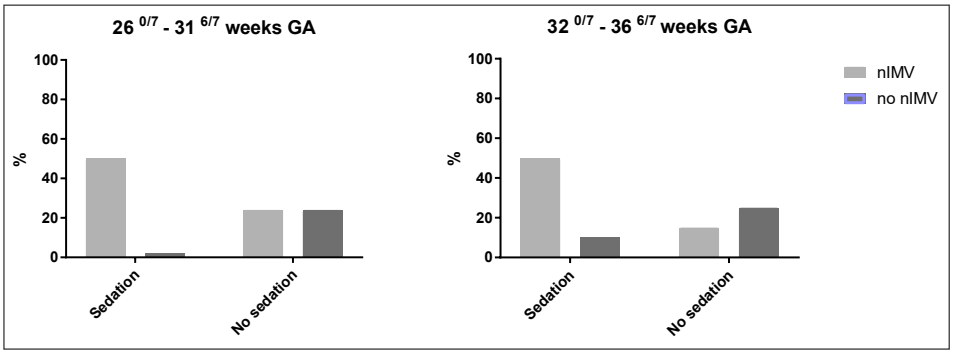

Figure 2 | Need for nasal intermittent mandatory ventilation (nIMV) during minimal invasive surfactant therapy

Only 1 infant in the sedated group was intubated during MIST, while 4 infants were intubated in the non-sedated group (1/42 (2%) vs 4/36 (11%), p=0.175). Overall, the rate of intubation in the first 24 hours after MIST was similar in the two groups (10/42 (24%) vs 6/36 (17%), p=0.576). GA stratum did not influence intubation rate.

The incidence of pneumothorax (3/42 (7%) vs 1/36 (3%); p=0.620) and pulmonary hemorrhage (1/42 (2%) vs 0/36 (0%), p=1.000) was not different. There were no differences in rates of intraventricular hemorrhage ≥ grade 3 or mortality. None of the included infants needed resuscitation during the MIST procedure.

DISCUSSION

In this randomized study we observed that during the MIST procedure more infants were comfortable and the average COMFORTneo score was lower when low-dose sedation was given. However, infants that received sedation were more likely to desaturate and receive nIMV. There were no differences in other complications of the procedure or the use of sedation. This implies that when accepting a temporary need for nIMV, low-dose sedation could be used to increase the comfort of preterm infants during the MIST procedure, without major clinical implications.

Resistance of the infant during laryngoscopy can lead to an increased risk of intraventricular hemorrhage by impairing cerebral venous return.(14-17) Therefore, more comfort during the procedure might be beneficial. The results of the meta-analyses of studies where no sedation is used, are conflicting.(21,22) While Kribs et al.(2007) and Klebermass-Schrehof et al.(2013) described a decrease in IVH, Aldana-Aguirre et al.(2016) reported no reduction in IVH. We have reported no differences in rate of IVH between the randomization groups, yet this trial was not powered on this outcome.

Cruz et al.(21) reported that infants in the NICU experience many invasive procedures each day, with the highest frequency in the vulnerable first week of life. Thereby, infants with the lowest GA and at the highest risk for neurological impairment received the lowest amount of analgesic interventions.(21) Procedural pain can affect neurodevelopment, as the exposure to multiple painful procedures can lead to on-going stress.(22) There is evidence that these adverse events can be prevented or minimized by using both analgesic and non-pharmacological interventions during painful procedures.(23, 24) On the other hand, the use of analgesia can lead to adverse effects in the brain as well.(25) A high level of analgesia correlates strongly with reduced cerebellar volume and poorer cognitive and motor outcomes in infancy.(26-28) However, in our study we used a single low dose of propofol, which reduced the stress of a painful stimulus in this vulnerable population and thereby might influenced neurodevelopment rather positively than negatively.

While this is the first trial focussing on sedation during MIST, the use of sedation for administrating surfactant by intubation-surfactant-extubation (INSURE) has previously been studied.(29) In both the INSURE and the MIST procedure, the sedative agent should have a rapid distribution and redistribution.(29, 30) Remifentanil is described to have these characteristics, and is therefore used in many clinical applications in neonates.(31) However, remifentanil was found to be unsuitable as premedication for INSURE, as it did not provide adequate sedation.(30) In addition, remifentanil is a potent respiratory depressant, which makes it unsuitable as a sedative for MIST.(31)

Propofol however, has been widely used as well during intubation and other procedures for sedation and anaesthesia.(32-34) Thereby, the level of sedation achieved by the use of propofol was considered satisfactory during surgery in the study of Piersigilli et al.(33), but this was not evaluated objectively.

One of the most noted side effects of propofol is the occurrence of hypotension, although the incidence varies in studies. Hypotension was not reported in the study which used a dose of 2 mg/kg propofol iv(35), while hypotension was reported in studies with an even lower dose of propofol.(36, 37) In our study, the observed rate of hypotension is similar to our previous observational report.(38) In most infants, hypotension was mild and transient and only 3/9 infants (33 %) needed a fluid bolus as treatment.

Only 44 % of infants receiving MIST in the study of Dargaville et al.(8) needed positive pressure ventilation, which we confirm in our non-sedated group (47 % needed nIMV). However, we report a significantly higher incidence of need for nIMV in the sedation group (93 %). This is due to a higher incidence of desaturation, which was comparable to the study of Descamps et al.(39) However, the incidence of need for intubation during or within 24 hours after the procedure, did not differ between the randomization groups, thereby indicating that the need for nIMV was transient.

Intermittent hypoxemia is associated with an impaired neurodevelopmental outcome.(40) However, infants born preterm are intrinsically at risk for intermittent hypoxic episodes during the first 6 - 8 weeks after birth due to immaturity and many other factors, with a mean of 100 - 800 hypoxic episodes occurring each week.(40) It is therefore difficult or even impossible to differentiate the effect of the single hypoxic episode during MIST procedure on outcome.

The neonatologists performing MIST in this trial were not blinded for the allocated treatment. Although there was clinical equipoise, awareness of the treatment allocation

could have influenced the use of nIMV. In contrast, the NICU nurses who analyzed the primary outcome were blinded, therefore this parameter was not influenced by the study design.

Another limitation of this study is the insufficient sample size to perform sub-analyses based on different GA strata. However, as we have included GA strata in the models for statistical analyses, our results are corrected for GA.

CONCLUSION

In this randomized controlled trial, we observed that preterm infants were more often comfortable during the MIST procedure while more often desaturation occurred and nIMV was given. The low dose sedation could help increase comfort during MIST and might reduce the risk for neurodevelopmental complications due to stress of a painful stimulus. However, only a large and adequately powered randomized trial on this significant clinical outcome can be conclusive on this statement.

REFERENCES

1. Kribs A. Minimally Invasive Surfactant Therapy and Noninvasive Respiratory Support. Clin Perinatol. 2016;43(4):755-71.
2. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB, et al. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med. 2008;358(7):700-8.
3. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants--2013 update. Neonatology. 2013;103(4):353-68.
4. Dargaville PA, Aiyappan A, De Paoli AG, Dalton RG, Kuschel CA, Kamlin CO, et al. Continuous positive airway pressure failure in preterm infants: incidence, predictors and consequences. Neonatology. 2013;104(1):8-14.
5. Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. BMJ. 2013;347:f5980.
6. Dargaville PA, Aiyappan A, Cornelius A, Williams C, De Paoli AG. Preliminary evaluation of a new technique of minimally invasive surfactant therapy. Arch Dis Child Fetal Neonatal Ed. 2011;96(4):F243-8.
7. Gopel W, Kribs A, Ziegler A, Laux R, Hoehn T, Wieg C, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. Lancet. 2011;378(9803):1627-34.
8. Dargaville PA, Aiyappan A, De Paoli AG, Kuschel CA, Kamlin CO, Carlin JB, et al. Minimally-invasive surfactant therapy in preterm infants on continuous positive airway pressure. Arch Dis Child Fetal Neonatal Ed. 2013;98(2):F122-6.
9. Anand KJ, Hall RW. Pharmacological therapy for analgesia and sedation in the newborn. Arch Dis Child Fetal Neonatal Ed. 2006;91(6):F448-53.
10. Kumar P, Denson SE, Mancuso TJ, Committee on F, Newborn SoA, Pain M. Premedication for nonemergency endotracheal intubation in the neonate. Pediatrics. 2010;125(3):608-15.
11. Barrington K. Premedication for endotracheal intubation in the newborn infant. Paediatr Child Health. 2011;16(3):159-71.
12. Milesi C, Baleine J, Mura T, Benito-Castro F, Ferragu F, Thiriez G, et al. Nasal midazolam vs ketamine for neonatal intubation in the delivery room: a randomised trial. Arch Dis Child Fetal Neonatal Ed. 2017.
13. Carbajal R, Eble B, Anand KJ. Premedication for tracheal intubation in neonates: confusion or controversy? Semin Perinatol. 2007;31(5):309-17.
14. Friesen RH, Honda AT, Thieme RE. Changes in anterior fontanel pressure in preterm neonates during tracheal intubation. Anesth Analg. 1987;66(9):874-8.
15. Pokela ML, Koivisto M. Physiological changes, plasma beta-endorphin and cortisol responses to tracheal intubation in neonates. Acta Paediatr. 1994;83(2):151-6.
16. Raju TN, Vidyasagar D, Torres C, Grundy D, Bennett EJ. Intracranial pressure during intubation and anesthesia in infants. J Pediatr. 1980;96(5):860-2.
17. Stow PJ, McLeod ME, Burrows FA, Creighton RE. Anterior fontanelle pressure responses to tracheal intubation in the awake and anaesthetized infant. Br J Anaesth. 1988;60(2):167-70.
18. Klotz D, Porcaro U, Fleck T, Fuchs H. European perspective on less invasive surfactant administration-a survey. Eur J Pediatr. 2017;176(2):147-54.
19. Caljouw MAA, Kloos, M.A.C., Olivier, M.Y., Heemskerk, I.W., Pison, W.C.R., Stigter, G.D. Measurement of pain in premature infants with a gestational age between 28-37 weeks: validation of the adapted COMFORT scale. J Neonatal Nurs. 2007;13.

20. Hassid S, Nicaise C, Michel F, Vialet R, Thomachot L, Lagier P, et al. Randomized controlled trial of sevoflurane for intubation in neonates. Paediatr Anaesth. 2007;17(11):1053-8.
21. Cruz MD, Fernandes AM, Oliveira CR. Epidemiology of painful procedures performed in neonates: A systematic review of observational studies. Eur J Pain. 2016;20(4):489-98.
22. Grunau RE, Holsti L, Peters JWB. Long-term consequences of pain in human neonates. Semin Fetal Neonat M. 2006;11(4):268-75.
23. Walter-Nicolet E, Annequin D, Biran V, Mitanchez D, Tourniaire B. Pain management in newborns: from prevention to treatment. Paediatric drugs. 2010;12(6):353-65.
24. Pillai Riddell R, Racine N, Turcotte K, Uman L, Horton R, Din Osmun L, et al. Nonpharmacological management of procedural pain in infants and young children: an abridged Cochrane review. Pain Res Manag. 2011;16(5):321-30.
25. McPherson C, Inder T. Perinatal and neonatal use of sedation and analgesia. Semin Fetal Neonatal Med. 2017;22(5):314-20.
26. Anand KJS, Hall RW, Desai N, Shephard B, Bergqvist LL, Young TE, et al. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. Lancet. 2004;363(9422):1673-82.
27. Simons SHP, van Dijk M, van Lingen R, Roofthooft D, Duivenvoorden HJ, Jongeneel N, et al. Routine morphine infusion in preterm newborns who received ventilatory support - A randomized controlled trial. Jama-J Am Med Assoc. 2003;290(18):2419-27.
28. Zwicker JG, Miller SP, Grunau RE, Chau V, Brant R, Studholme C, et al. Smaller Cerebellar Growth and Poorer Neurodevelopmental Outcomes in Very Preterm Infants Exposed to Neonatal Morphine. Journal of Pediatrics. 2016;172:81-+.
29. de Kort EH, Reiss IK, Simons SH. Sedation of newborn infants for the INSURE procedure, are we sure? Biomed Res Int. 2013;2013:892974.
30. de Kort EH, Hanff LM, Roofthooft D, Reiss IK, Simons SH. Insufficient Sedation and Severe Side Effects after Fast Administration of Remifentanil during INSURE in Preterm Newborns. Neonatology. 2017;111(2):172-6.
31. Kamata M, Tobias JD. Remifentanil: applications in neonates. J Anesth. 2016;30(3):449-60.
32. Shah PS, Shah VS. Propofol for procedural sedation/anaesthesia in neonates. Cochrane Database Syst Rev. 2011(3):CD007248.
33. Piersigilli F, Di Pede A, Catena G, Lozzi S, Auriti C, Bersani I, et al. Propofol and fentanyl sedation for laser treatment of retinopathy of prematurity to avoid intubation. J Matern Fetal Neonatal Med. 2017:1-5.
34. Smits A, Thewissen L, Caicedo A, Naulaers G, Allegaert K. Propofol Dose-Finding to Reach Optimal Effect for (Semi-)Elective Intubation in Neonates. J Pediatr. 2016;179:54-60 e9.
35. Nauta M, Onland W, De Jaegere A. Propofol as an induction agent for endotracheal intubation can cause significant arterial hypotension in preterm infants. Paediatr Anaesth. 2011;21(6):711-2.
36. Simons SH, van der Lee R, Reiss IK, van Weissenbruch MM. Clinical evaluation of propofol as sedative for endotracheal intubation in neonates. Acta Paediatr. 2013;102(11):e487-92.
37. Welzing L, Kribs A, Eifinger F, Huenseler C, Oberthuer A, Roth B. Propofol as an induction agent for endotracheal intubation can cause significant arterial hypotension in preterm neonates. Paediatr Anaesth. 2010;20(7):605-11.
38. Dekker J, Lopriore E, Rijken M, Rijntjes-Jacobs E, Smits-Wintjens V, Te Pas A. Sedation during Minimal Invasive Surfactant Therapy in Preterm Infants. Neonatology. 2016;109(4):308-13.
39. Descamps CS, Chevallier M, Ego A, Pin I, Epiard C, Debillon T. Propofol for sedation during less invasive surfactant administration in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2017;102(5):F465.
40. Martin RJ, Wang K, Koroglu O, Di Fiore J, Kc P. Intermittent hypoxic episodes in preterm infants: do they matter? Neonatology. 2011;100(3):303-10.