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Stimulating and maintaining spontaneous breathing of preterm infants at birth

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Citation
Dekker, J. (2019, September 10). *Stimulating and maintaining spontaneous breathing of preterm infants at birth*. Retrieved from https://hdl.handle.net/1887/77439

Version:	Not Applicable (or Unknown)
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Note: To cite this publication please use the final published version (if applicable).

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Author: Dekker, J.
Title: Stimulating and maintaining spontaneous breathing of preterm infants at birth
Issue Date: 2019-09-10

CHAPTER 8

Sedation during minimal invasive surfactant therapy in preterm infants

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Neonatology 2016;109:308-313

ABSTRACT

BACKGROUND

There is no data available whether sedation should be given during minimally invasive surfactant therapy (MIST). The aim of this study was to compare the level of comfort of preterm infants receiving sedation vs no sedation for MIST.

METHODS

A retrospective study of preterm infants receiving MIST was performed in the Leiden University Medical Center in 2014. Sedation (propofol 1 mg/kg) was optional and left to the discretion of the caregiver. Standardized COMFORTneo scores were compared and COMFORTneo < 14 was considered comfortable. Basic characteristics and complications were noted.

RESULTS

In 38 infants receiving MIST, 23 received propofol and 15 were not sedated. Mean ± SD gestational age (29 ± 2 weeks vs 29 ± 3 weeks) and birth weight (1312 ± 483 grams vs 1469 ± 588 grams) were not different. Median (IQR) COMFORTneo was not different between the groups before (11 (9 - 15) vs 10 (8 - 12)) and after MIST (10 (8 - 12) vs 9 (8 - 10)), but lower in the sedated group during MIST (12 (9 - 17) vs 20 (15 - 23), p=0.002) with more often COMFORTneo < 14 (56% vs 11%, p=0.04). Duration of MIST (2 (2 - 4) minutes vs 3 (2 - 7) minutes) and occurrence of bradycardia (13% vs 33%) and hypotension (21% vs 18%) were not different. Although not significant, intubation occurred more often in the sedated group (during MIST: 9% vs 0%, < 24 hours after MIST: 26% vs 13%). During MIST, oxygen saturation < 80% lasted longer in the sedated group (3 (2 - 4) minutes vs 1 (0 - 2) minutes, p=0.001) and nasal intermittent positive pressure ventilation (nIPPV) was applied more (100% vs 33%, p<0.001).

CONCLUSION

Preterm infants receiving MIST were more comfortable when sedation was given, but needed ventilation more often. A randomized controlled trial is warranted to test whether the benefit of sedation outweighs the risks of complications.

INTRODUCTION AND RATIONALE

Many preterm infants need surfactant therapy to diminish alveolar surface tension and work of breathing caused by respiratory distress syndrome (RDS), so as to avoid the occurrence of atelectasis.(1) While intubation and mechanical ventilation is increasingly being avoided(2, 3), infants are still being intubated and mechanically ventilated for surfactant therapy.(4) Mechanical ventilation can, however, lead to lung injury and ultimately to bronchopulmonary dysplasia (BPD).(5) The incidence of BPD decreases when non-invasive ventilation increases.(6) In this context, minimal invasive surfactant therapy (MIST) techniques are promising, in which surfactant is administered to a spontaneously breathing infant who then remains on continuous positive airway pressure (CPAP).(7, 8) During MIST, the vocal cords are visualized by the use of a laryngoscope and the trachea is catheterized using a semirigid catheter, and then the surfactant is instilled.(4) To date, most Neonatal Intensive Care Unit (NICU) centers in the Netherlands have adopted this procedure.

There is consensus that an endotracheal intubation procedure should be performed while the infant is adequately sedated.(9, 10) However, there is an ongoing debate whether or not sedation should be used during MIST as the presence of spontaneous breathing is a pre-requisite for the procedure. So far, there are no studies concerning sedation during this procedure. In the recent published studies and current trials on MIST, no sedation is given before MIST.(4)

By using a laryngoscope during MIST, pharyngeal stretching triggers sympathic and parasympathetic reflexes, which could lead to cardiovascular responses.(10) Also, when the infant is not sedated, efforts to resist the laryngoscope and attempts to cry can cause an increase in intracranial pressure, which could result in impairment of the venous return of the brain and intracranial venous hypertension.(9, 11, 12) This can then contribute to the risk of intraventricular hemorrhage.(9) In addition, laryngoscopy is associated with apnea, increased blood pressure, decreased heart rate and decreased transcutaneous PO_2.(13-15) These differences in vital signs were greater in infants who did not receive any premedication.(15) However, many analgesic agents used for neonatal intubation have been studied, and side effects such as respiratory depression, hypotension, muscle rigidity, increased intracranial blood pressure and decreased cerebral blood flow have been reported.(16, 17)

Propofol is routinely used as premedication for endotracheal intubation at our center. Although the maintenance of spontaneous breathing is described as an advantage of propofol, hypotension and respiratory depression have been reported.(17)

The use of propofol during MIST is currently left to the discretion of the attending neonatologist when discomfort is anticipated. Propofol may then contribute to more comfort and less resistance from the infant during the procedure, which can increase the success of the procedure. However, administering propofol could also cause respiratory depression and increase the chance for non-invasive intermittent positive pressure ventilation or, when respiratory depression persists, intubation and mechanical ventilation. There is no data available whether the use of propofol for more comfort during MIST outweighs the risk for failure of the procedure and the occurrence of complications.

We performed a cohort study to compare the level of comfort and the occurrence of complications of infants receiving sedation with infants receiving no premedication during MIST.

METHODS

A retrospective cohort study was conducted at the neonatal department of the Leiden University Medical Center. All admitted infants receiving surfactant by MIST in the year 2014 were included in this study. We only included the first MIST, repeated surfactant doses by MIST were excluded. The criteria receiving surfactant by MIST were: GA 25^{+6} – 36^{+6} weeks of gestation, no need for imminent intubation, adequate respiratory drive, CPAP level ≥ 8 cm H_2O and FiO_2 > 0.3.

According to the local protocol the decision whether to give sedation for MIST was left to the discretion of the attending neonatologist. For endotracheal intubation, intravenous propofol 2.5 mg/kg is standardly used for sedation in our unit. However, to maintain spontaneous breathing and reduce the risk of side effects, a reduced dose of intravenous propofol (1 mg/kg) was administered before MIST. In each infant, non-pharmacological techniques for comfort were also performed, which consisted of the administration of oral sucrose 24% in the cheek pouch of the infant along with a pacifier at least 2 minutes before the procedure, and swaddling the infant in a swaddling cloth to keep the infant contained.

MIST was performed using the method as described earlier by Dargaville et al.(8), in which the vocal cords are visualized using a laryngoscope, where after a semi-rigid angiocatheter is orally introduced to catheterize the trachea.

The infants receiving propofol (sedated group) were compared with the infants without premedication (non-sedated group). Nurses in our unit routinely score the comfort of the infants using the COMFORTneo score, which is validated for measuring objectively the (dis)comfort of a preterm infant.(18) Interrater reliability was assessed by Caljouw et al.(18), who found that the COMFORTneo score is reliable to measure distress in preterm infants. With a score < 14, the infant's comfort is considered to be acceptable. The COMFORTneo score before, during and after MIST of both groups were retrieved and noted. In our unit, interrater reliability between nurses of the COMFORTneo research group (Caljouw et al.(18)) and other NICU nurses was assessed in ten clinical situations, and nurses could measure comfort using the COMFORTneo score if they had achieved a Cohen's $\kappa > 0.6$. Cohen's κ measures the interrater agreement, where 0 means no agreement and 1 means total agreement.(19)

Both COMFORTneo scores and basic characteristics (gestational age, gender and birth weight) were gathered, as well as complications of MIST and the administration of propofol. These complications included the need for nIPPV, intubation, the occurrence of desaturation (oxygen saturation < 80 %), hypotension (mean mmHg < gestational age) or bradycardia (heart rate < 80 bpm). The differences in heart rate between the interval before the MIST and during the MIST were also compared for the sedated and the non-sedated groups.

All study data were retrieved from the digital medical charts (PDMS, MetaVision iMDsoft, Leiden, The Netherlands), a clinical information system designed especially for use in NICUs. In this system, each parameter is noted every minute.

This was a retrospective study and did not need to comply with the Dutch law on Medical Research in Humans; the Research Ethics Committee issued a statement of no objection.

Statistical analysis

Because of the retrospective nature of this study, a convenience sample was used. No power calculation was performed because there was no data regarding sedation during MIST. Statistical analysis was performed using SPSS 22 (IBM SPSS Statistics). The parameters of both groups were tested for normality using Kolmogorov-Smirnov and Shapiro-Wilkinson. The groups were compared using Student's t-test for parametric variables and the Mann-Whitney U test for non-parametric comparisons for continuous variables, and the X^2 test for categorical variables. Results are presented as mean ± SD for normally distributed values or median (IQR) for non-normally distributed values. $P < 0.05$ was considered statistically significant. Reported p-values are two-sided.

RESULTS

During the one-year period, 310 infants with a gestational age between 26^{+0} and 36^{+6} weeks were admitted to the NICU. In 38 infants, surfactant was given by MIST, of which 23 infants received propofol (supplemental video 1; www.karger.com/doi/10.1159/000443823) and 15 infants were not sedated (supplemental video 2) based on the discretion of the attending neonatologist. Reasons given for prescribing propofol were expected discomfort. There were no significant differences in mean ± SD gestational age (sedation vs no sedation: 29 ± 2 weeks vs 29 ± 3 weeks), birth weight (1312 ± 483 grams vs 1469 ± 588 grams) and the percentage of males (61% (14/23) vs 73% (11/15)). The median (IQR) duration of the procedure did not significantly differ between the groups (2 (2 - 4) minutes vs 3 (2 - 7) minutes).

Comfort

Surfactant was administered by MIST 38 times, in which comfort was scored before, during and after the procedure in 76% (29/38), 71% (27/38) and 71% (27/38) of the procedures, respectively. Both before and after MIST the median (IQR) COMFORTneo score did not differ between the study groups, but the COMFORTneo score during the procedure was significantly lower in the sedated group when compared to the non-sedated group (Table 1). The COMFORTneo score was significantly more often < 14 in the sedated group during MIST (56% vs 11%, $p<0.05$). There was a significant positive correlation between both gestational age ($r=0.419$, $p<0.05$) as postnatal age ($r=0.435$, $p<0.05$) and COMFORTneo score during the procedure. However, as previously mentioned the gestational age did not differ between the sedated and the not sedated group.

Table 1 | Results: comfort

	Sedated group n = 23	Non-sedated group n = 15	*p*-value
COMFORTneo score before MIST	11 (9 – 15) *n = 18*	10 (8 – 12) *n = 11*	ns
COMFORTneo score during MIST	12 (9 – 17) *n = 17*	20 (15 – 23) n = 10	0.002
% COMFORTneo score < 14 during MIST	9/16 (56%)	1/9 (11%)	0.04
COMFORTneo score after MIST	10 (8 – 12) *n = 23*	9 (8 – 10) *n = 9*	ns

Data is presented as median (IQR) for non-parametric data, and n (%) for categorical data.

Complications

The occurrence of complications could be retrieved from the digital medical chart for all patients. Bradycardia and hypotension occurred in a few infants, but these were not significantly different between the groups (Table 2). There was no significant increase or decrease in heart rate during the procedure in both groups. The median (IQR) duration of oxygen desaturation of all infants (< 80 %) was longer in the sedated group (3 (2 - 4) minutes vs 1 (0 - 2) minutes, p <0.01). All patients in the sedated group needed nIPPV temporarily due to apnea and saturation < 80 % during MIST as compared to 33 % in the non-sedated group (p<0.001) (Table 2). 2 infants (8%) in the sedated group were intubated during MIST due to failure of the procedure because the trachea could not be catheterized, while this did not occur in the non-sedated group (ns). There was no significant difference in occurrence of intubations in the first 24 hours after MIST between the two groups (Table 2). The intubated infants had a mean ± SD gestational age of 28 ± 2 weeks and a birth weight of 1109 ± 454 grams. Reasons to intubate in the first 24 hours after MIST were apneas in 3 cases, no improvement or an increase in FiO_2 need in 3 cases, and no adequate respiratory drive before the procedure with persistent apnea after the procedure in 2 cases (Table 3).

Table 2 | Results: complications

	Sedated group n = 23	Non-sedated group n = 15	*p*-value
nIPPV during MIST[a]	23/23 (100%)	5/15 (33%)	< 0.001
Intubation in the first 24 hours after MIST[a]	6/23 (26%)	2/15 (13%)	ns
Intubation during MIST[a]	2/23 (9%)	0/15 (0%)	ns
Duration of SpO_2 < 80% during MIST (minutes)[b]	3 (2 – 4)	1 (0 – 2)	0.001
Hypotension during MIST[a]	3/14 (21%)	2/11 (18%)	ns
Bradycardia during MIST[a]	3/23 (13%)	5/15 (33%)	ns
Heartrate before – during MIST (bpm)[b]	-4 (-10 - -1)	-2 (-7 – 3)	ns

Data is presented as n (%) for categorical data (a) and median (IQR) for non-parametric data (b).

Table 3 | Reasons for intubation

	Sedated group n = 8	Non-sedated group n = 2	*p*-value
Trachea could not be catheterized	2/8 (25%)	0/2 (0%)	ns
Infant did not meet MIST criteria before procedure	2/8 (25%)	0/2 (0%)	ns
Apnea	2/8 (25%)	1/2 (50%)	ns
No improvement/increase FiO_2 needed	2/8 (25%)	1/2 (50%)	ns

Data is presented as n (%) for categorical data.

DISCUSSION

In this retrospective cohort study, we observed that infants receiving propofol had a higher level of comfort compared to the infants receiving no sedation before MIST. However, infants receiving propofol desaturated for a longer period, needed temporarily nIPPV more frequently during the procedure and, although this did not reach significance, more often infants were intubated during or within 24 hours after MIST. All other complications (hypotension and bradycardia) were not different between the groups.

Administration of surfactant without intubation and mechanical ventilation, using procedures such as MIST, has recently received increased attention and many neonatal units have adopted the method.(4, 7, 20, 21) There is however no consensus on whether the procedure should be performed with or without the use of premedication, which has been a hot topic for debate. This is the first study describing the comfort of preterm infants receiving MIST using objective measurements and the effect of sedation vs no sedation. It is argued by Dargaville et al(4) that MIST can generally be performed without creating discomfort in the infants, however, this was not objectively evaluated. There is consensus that an intubation procedure should be performed while the infant is adequately sedated.(9, 10) Laryngoscopy can be painful and is associated with crying and increased changes in intracranial pressure when infants are awake.(9, 11, 12) It could be reasoned that this also accounts for MIST as laryngoscopy is also performed.

Although propofol has been used for the intubation-surfactant-extubation (INSURE) method, its usage for MIST has not been described before.(17) Propofol is used because of its short acting character and it is also used in our unit as sedation for endotracheal intubation. We have chosen to use a low dose of propofol for MIST to minimize the risk of apnea and hypotension. Propofol has an anxiolytic effect in low dosages, but it is not known whether propofol has analgesic effects or not.(22) Propofol is effective for obtaining hypnosis and muscle relaxation in endotracheal intubation.(16, 17) One of the complications of propofol is respiratory depression.(17) This study has shown that all infants receiving propofol needed nIPPV temporarily, compared to 33 % of infants receiving no propofol. However, respiratory drive might be depressed by the use of propofol; of all sedated infants, 2/23 infants (9 %) needed to be intubated during the procedure due to other reasons than respiratory depression, as the trachea could not be catheterized. To make solid conclusions about respiratory depression caused by propofol for MIST, a randomized controlled trial is warranted.

When high doses of propofol were used (3 and 6 mg/kg), hypotension was considered a significant complication during and within 1 hour after intubation.(23, 24) In contrast, other studies reported that hypotension did not occur when propofol 2.5 mg/kg was used.(16, 25) Interestingly, Welzing et al.(17) also noted a high incidence of hypotension even when a dosage of 1 mg/kg was used. However, our study does not confirm this as we did not observe more hypotension when we used this low dose compared to no sedation.

The MIST procedure has been recently introduced in our unit and it is possible that infants would be more comfortable in a center with extensive experience in the procedure. However, the MIST procedures in our study were performed by neonatologists who were well trained in endotracheal intubation and laryngoscopy. Also, there were no significant differences in duration of the procedure and the frequency of complications in the non-sedated group appeared to be low.

The decision for the use of propofol as premedication for MIST was left to the discretion of the attending neonatologist, and a selection bias could have occurred. The reason given by the caregivers for the decision to use propofol was expected discomfort. However, gestational age, birth weight and COMFORT score before the procedure were not different between the groups, which makes it less likely that these items influenced the decision of the caregiver to give sedation or not.

This was a small retrospective cohort study with a convenience sample. We already reached a large difference in COMFORTneo score in this small group, but it is possible that differences in complications would have reached significance in a larger group. Although we could not retrieve the COMFORTneo score in all infants, this was equally distributed among the study groups. In addition, comfort was scored by nurses who were not blinded to the treatment given, which could influence the COMFORTneo scores and cause observer bias.

CONCLUSION

In summary, we observed more comfort in preterm infants when they received a low dose of propofol (1 mg/kg) as premedication for MIST, but an increase in respiratory complications and non-significantly more intubations. However, we do not consider this study to be conclusive and a randomized controlled trial is warranted to determine whether the benefit of sedation in comfort outweighs the risks for complications.

REFERENCES

1. Wang L, Chen L, Li R, Zhao J, Wu X, Li X, et al. Efficacy of surfactant at different gestational ages for infants with respiratory distress syndrome. Int J Clin Exp Med. 2015;8(8):13783-9.
2. Dunn MS, Kaempf J, de Klerk A, de Klerk R, Reilly M, Howard D, et al. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics. 2011;128(5):e1069-76.
3. 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.
4. 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.
5. Mokres LM, Parai K, Hilgendorff A, Ertsey R, Alvira CM, Rabinovitch M, et al. Prolonged mechanical ventilation with air induces apoptosis and causes failure of alveolar septation and angiogenesis in lungs of newborn mice. Am J Physiol Lung Cell Mol Physiol. 2010;298(1):L23-35.
6. Kribs A, Hartel C, Kattner E, Vochem M, Kuster H, Moller J, et al. Surfactant without intubation in preterm infants with respiratory distress: first multi-center data. Klin Padiatr. 2010;222(1):13-7.
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, 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.
9. Friesen RH, Honda AT, Thieme RE. Changes in anterior fontanel pressure in preterm neonates during tracheal intubation. Anesth Analg. 1987;66(9):874-8.
10. Pokela ML, Koivisto M. Physiological changes, plasma beta-endorphin and cortisol responses to tracheal intubation in neonates. Acta Paediatr. 1994;83(2):151-6.
11. 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.
12. 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.
13. Kelly MA, Finer NN. Nasotracheal intubation in the neonate: physiologic responses and effects of atropine and pancuronium. J Pediatr. 1984;105(2):303-9.
14. Marshall TA, Deeder R, Pai S, Berkowitz GP, Austin TL. Physiologic changes associated with endotracheal intubation in preterm infants. Crit Care Med. 1984;12(6):501-3.
15. Millar C, Bissonnette B. Awake intubation increases intracranial pressure without affecting cerebral blood flow velocity in infants. Can J Anaesth. 1994;41(4):281-7.
16. Ghanta S, Abdel-Latif ME, Lui K, Ravindranathan H, Awad J, Oei J. Propofol compared with the morphine, atropine, and suxamethonium regimen as induction agents for neonatal endotracheal intubation: a randomized, controlled trial. Pediatrics. 2007;119(6):e1248-55.
17. 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.
18. Caljouw MAA, Kloos MAC, Olivier MY, Heemskerk IW, Pison WCR, Stigter GD, et al. Measurement of pain in premature infants with a gestational age between 28-37 weeks: validation of the adapted COMFORT scale. J Neonatal Nurs. 2007;13:13-8.

19. Altman D. Practical Statistics for Medical Research. Hall Ca, editor. New York: CRC Press; 1999.
20. Aguar M, Cernada M, Brugada M, Gimeno A, Gutierrez A, Vento M. Minimally invasive surfactant therapy with a gastric tube is as effective as the intubation, surfactant, and extubation technique in preterm babies. Acta Paediatr. 2014;103(6):e229-33.
21. More K, Sakhuja P, Shah PS. Minimally invasive surfactant administration in preterm infants: a meta-narrative review. JAMA Pediatr. 2014;168(10):901-8.
22. Kotani Y, Shimazawa M, Yoshimura S, Iwama T, Hara H. The experimental and clinical pharmacology of propofol, an anesthetic agent with neuroprotective properties. CNS Neurosci Ther. 2008;14(2):95-106.
23. Vanderhaegen J, Naulaers G, Van Huffel S, Vanhole C, Allegaert K. Cerebral and systemic hemodynamic effects of intravenous bolus administration of propofol in neonates. Neonatology. 2010;98(1):57-63.
24. 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.
25. 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.