READY TO TACK

Improving the use of premedication
to promote patient safety and comfort
during endotracheal intubation in neonates

Ellen de Kort

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Een wijziging van koers

Verbetering in het gebruik van premedicatie ter bevordering
van de patiëntveiligheid en het comfort tijdens endotracheale
intubatie van pasgeborenen

Proefschrift

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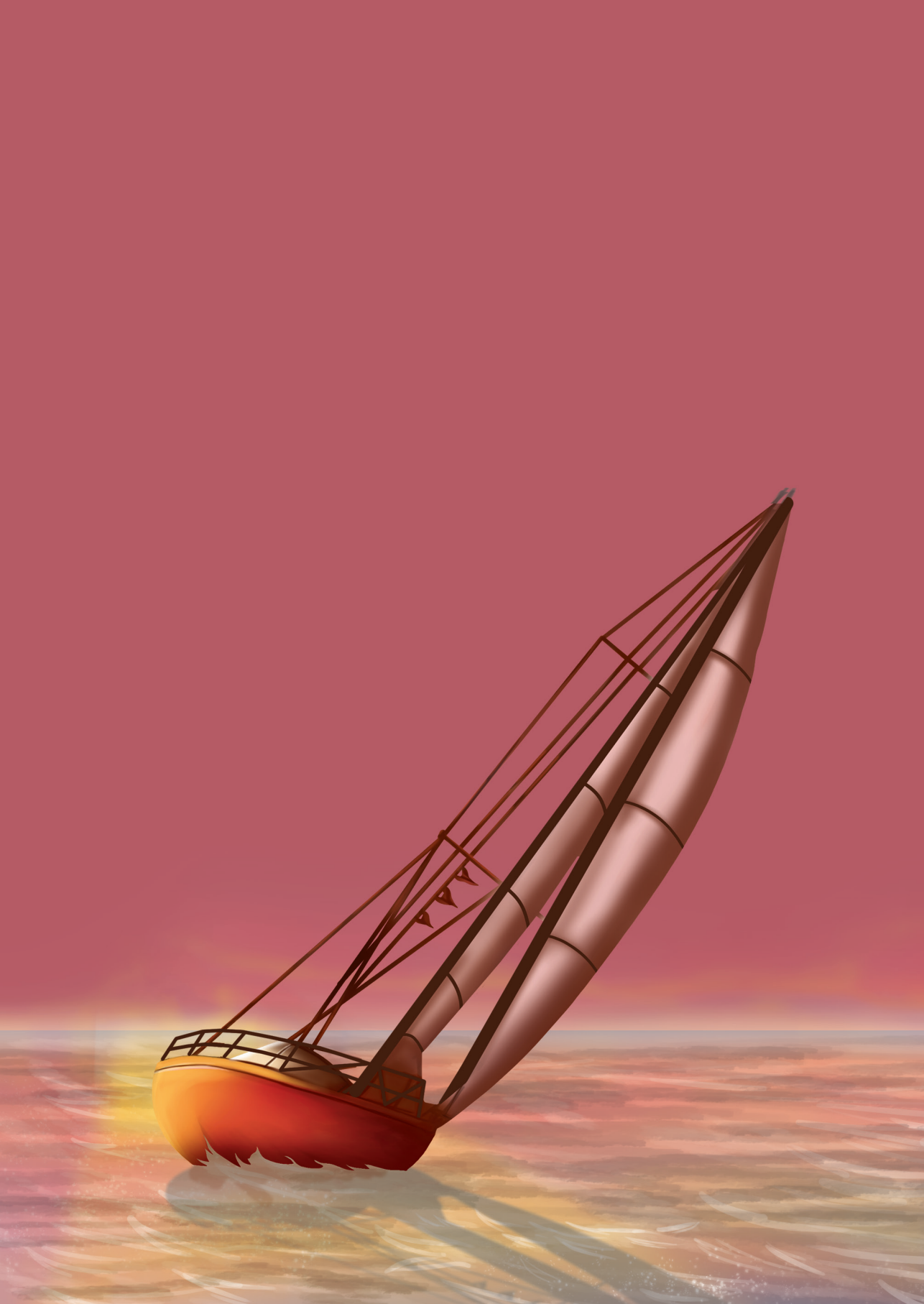
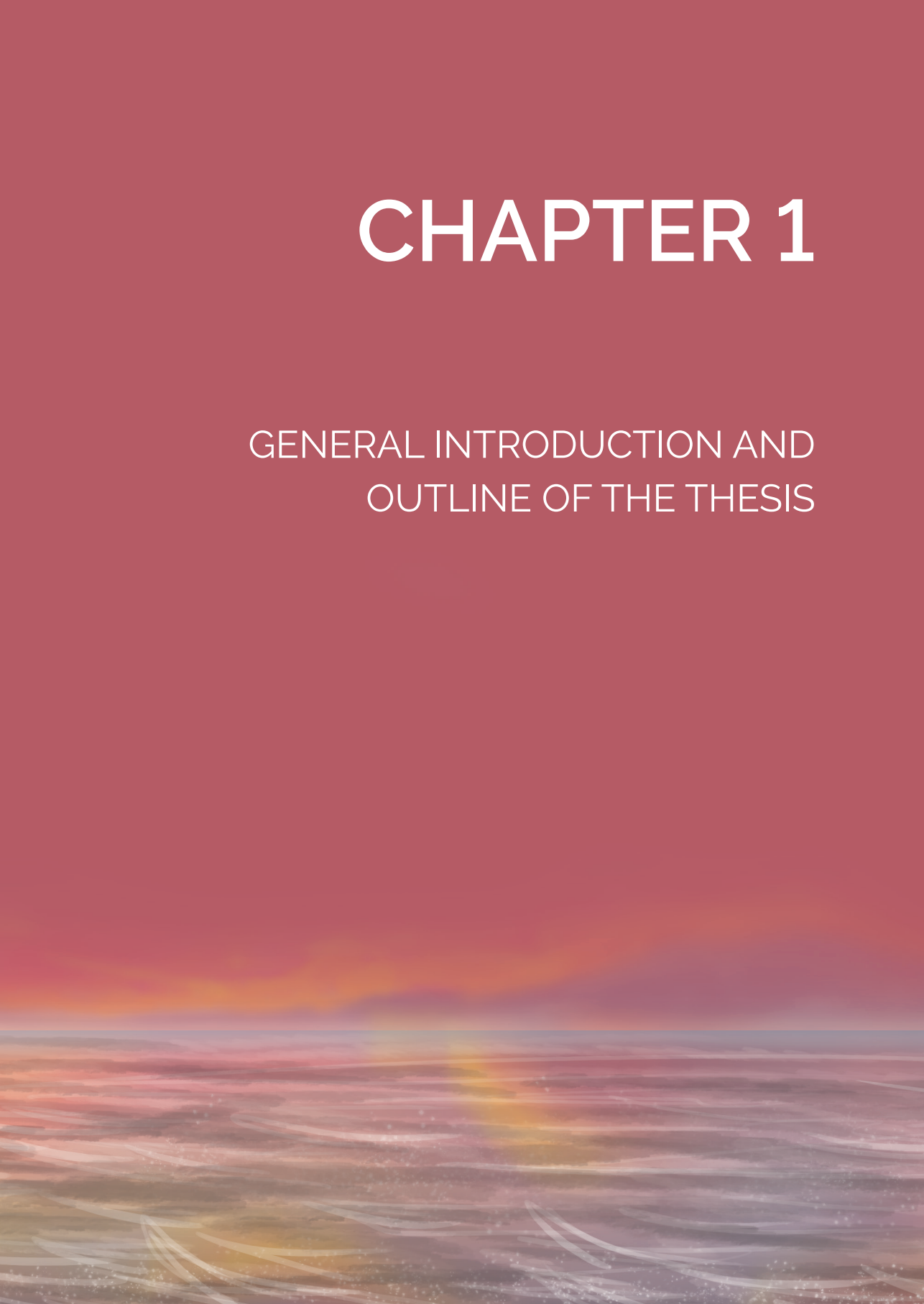


CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS



GENERAL INTRODUCTION

In the early 1980's the first reports appeared in the literature describing the harmful effects of performing endotracheal intubation in neonates without the use of premedication. In an observational trial in 10 preterm infants, Marshall et al. examined the physiological changes that were associated with awake endotracheal intubation. The authors observed a decrease in heart rate and transcutaneous oxygen tension, and an increase in systolic blood pressure during laryngoscopy and placement of the endotracheal tube.[1] Shortly after this, Kelly et al. were the first to perform a randomized controlled trial in which awake intubation in neonates was compared to intubation with the use of premedication. They reported a significantly lower increase in intracranial pressure and less decrease in heart rate in infants who were treated with pancuronium and atropine before intubation, compared to infants who received only atropine or no premedication.[2]

After these reports, a number of studies evaluated the effects of different premedication strategies compared to awake intubation. Results of these reports showed that awake intubation resulted in a greater increase in intracranial pressure,[2-6] elevated systemic blood pressure,[5-8] tachycardia,[3,7] bradycardia[2,9] and hypoxemia[10] compared to the administration of premedication prior to endotracheal intubation. Awake intubation also resulted in a longer duration to complete successful intubation and a higher number of intubation attempts.[7-11] In 2001, this knowledge about the harmful effects of awake intubation resulted in a consensus statement on the prevention and management of pain in the newborn. It was stated that endotracheal intubation should only be performed without analgesia or sedation for resuscitation in the delivery room or in emergency situations without the availability of an intravenous access.[12] In all other situations, premedication should be used during neonatal intubation.

At that time, the routine use of premedication prior to nonemergency intubation was only around 40% in several countries.[13-15] After the harmful effects of awake intubation became apparent, the routine use of premedication for nonemergency endotracheal intubation became subject of extensive research all around the world. In the last 20 years, a tremendous increase in the routine use of premedication up to around 90% was seen.[16-19] Despite the increased use of premedication, there was extensive variability in the drugs that were used as premedication and their dosages.[13,16,17,19-21]

An ideal premedication strategy for endotracheal intubation in newborns should eliminate pain and discomfort, minimize the physiological abnormalities that can accompany laryngoscopy and intubation, prevent trauma to the airway and provide circumstances to perform a successful procedure as quickly as possible. Besides this,

the premedication regimen should have a rapid onset and a short duration of action, and possess no substantial side effects. The American Academy of Pediatrics suggested the ideal premedication strategy to consist of a vagolytic drug to prevent bradycardia, an analgesic or hypnotic drug to control pain and/or reduce the level of consciousness, and a muscle relaxant to provide ideal intubating conditions.[22-24] In the last decade, however, the focus changed more and more towards research into a single drug regimen such as propofol, remifentanil or fentanyl. Today, almost 40 years after the first report on the harmful effects of awake endotracheal intubation, the optimal premedication strategy for endotracheal intubation in newborns is still not known.[25]

Even with the use of premedication, endotracheal intubation in newborns remains a difficult and high-risk procedure that often requires multiple attempts for successful completion. The overall first attempt success rate is only about 50%, with variations depending on the level of experience of the provider.[26-33] Several studies have shown that endotracheal intubation is frequently accompanied by severe and non-severe adverse events.[26,31,34-36] These data suggest that there is an urgent need to improve success and safety in neonatal endotracheal intubations.

Although patients within the field of neonatology seem rather uniform, there are remarkable differences between the larger late preterm and term born neonates on one side and the much smaller very and extremely preterm infants on the other side. These differences lie for example in the underlying diseases causing respiratory insufficiency, and in the risk of developing ventilator-induced lung injury and bronchopulmonary dysplasia (BPD). In late preterm and term born neonates respiratory distress is mostly caused by perinatal associated complications, for example asphyxia, group B streptococcus infection/pneumonia or meconium aspiration syndrome. These diseases have a longer duration of recovery and, therefore, often need mechanical ventilation for a period of several days or more. Despite this, the risk of ventilator-induced lung injury for this category of patients is limited.

Although in smaller preterm infants diseases such as infection, pneumonia or necrotizing enterocolitis are also frequent causes of respiratory insufficiency, one of the major conditions for respiratory insufficiency is respiratory distress syndrome (RDS).[37] A substantial part of the preterm population requires surfactant therapy for RDS, which is historically administered as a bolus via the endotracheal tube during a period of mechanical ventilation.[38] Mechanical ventilation in preterm infants can further disrupt alveolarization and growth of the pulmonary vasculature, and activate inflammatory pathways which can lead to damage to the preterm lung. Eventually, this can result in BPD.[39]

The last decades there has been a tremendous increase in the use of non-invasive ventilatory strategies in preterm newborns. In accordance with these developments, lesser invasive methods of surfactant administration limiting the period of mechanical ventilation have emerged. The first technique used in clinical practice, was the INtubation – SURfactant – Extubation (INSURE) method. In this method, patients were intubated for the sole purpose of surfactant administration and were extubated as soon as possible thereafter.[40] Compared to surfactant administration during mechanical ventilation, INSURE decreased the need for mechanical ventilation, and the incidence of BPD and air leak syndromes.[41] INSURE, however, still requires a short period of mechanical ventilation and even these brief periods have the possibility of causing lung injury.[39,42]

After that, several techniques to administer surfactant without the need for mechanical ventilation were developed. One of these techniques is the use of a thin catheter to administer surfactant to spontaneously breathing infants on nasal Continuous Positive Airway Pressure (nCPAP), a technique known as 'Less Invasive Surfactant Administration' (LISA) or 'Minimally Invasive Surfactant Therapy' (MIST).[43,44] This thin catheter technique has been shown to reduce the incidence of death or BPD, lower the need for mechanical ventilation, and shorten the duration of mechanical ventilation, oxygen therapy and different kinds of respiratory support.[45-51] In the past decade, LISA has made its way into clinical practice to a more or less extent.[52-56] The characteristics of the INSURE and LISA procedures and their differences with surfactant therapy during mechanical ventilation are outlined in Figure 1.

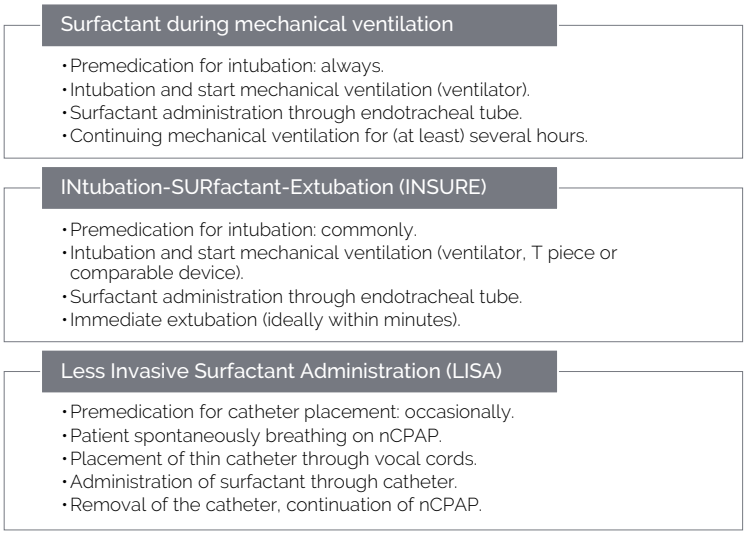


Figure 1. Characteristics of different techniques to administer surfactant

In both INSURE and LISA, laryngoscopy is performed and an endotracheal tube (INSURE) or thin catheter (LISA) is placed through the vocal cords. Both procedures, therefore, have considerable similarities with the procedure of endotracheal intubation for the purpose of mechanical ventilation. Likely, the harmful effects of performing INSURE or LISA in awake patients are comparable with the harmful effects of performing awake intubation. Ideally, during INSURE and LISA premedication should be used. Studies on the use of INSURE do report on the use of various drugs as premedication.[40,57-67] LISA, however, is often performed without the use of premedication.[44,49,51-56] The choice of premedication for these procedures should be carefully made. A very short period of action to facilitate rapid extubation in case of INSURE and complete preservation of the respiratory drive in case of LISA are of utmost importance for success of both procedures.

CONTENTS OF THIS THESIS

The overall aim of this thesis was to increase patient safety and comfort during endotracheal intubation in newborn infants by optimizing the use of premedication. The specific aims of this thesis were:

1. Premedication use during INSURE and LISA: to find the most optimal premedication strategy for the INSURE procedure and to evaluate the need for premedication use during LISA by describing the effects of performing LISA without premedication.
2. Measurement of the effect of premedication: to standardize the intubation procedure by developing an objective scoring system to determine level of sedation after the administration of premedication.
3. Propofol as premedication: to find suitable doses of propofol that provide optimal sedation without significant side effects in newborns of different gestational and postnatal ages.

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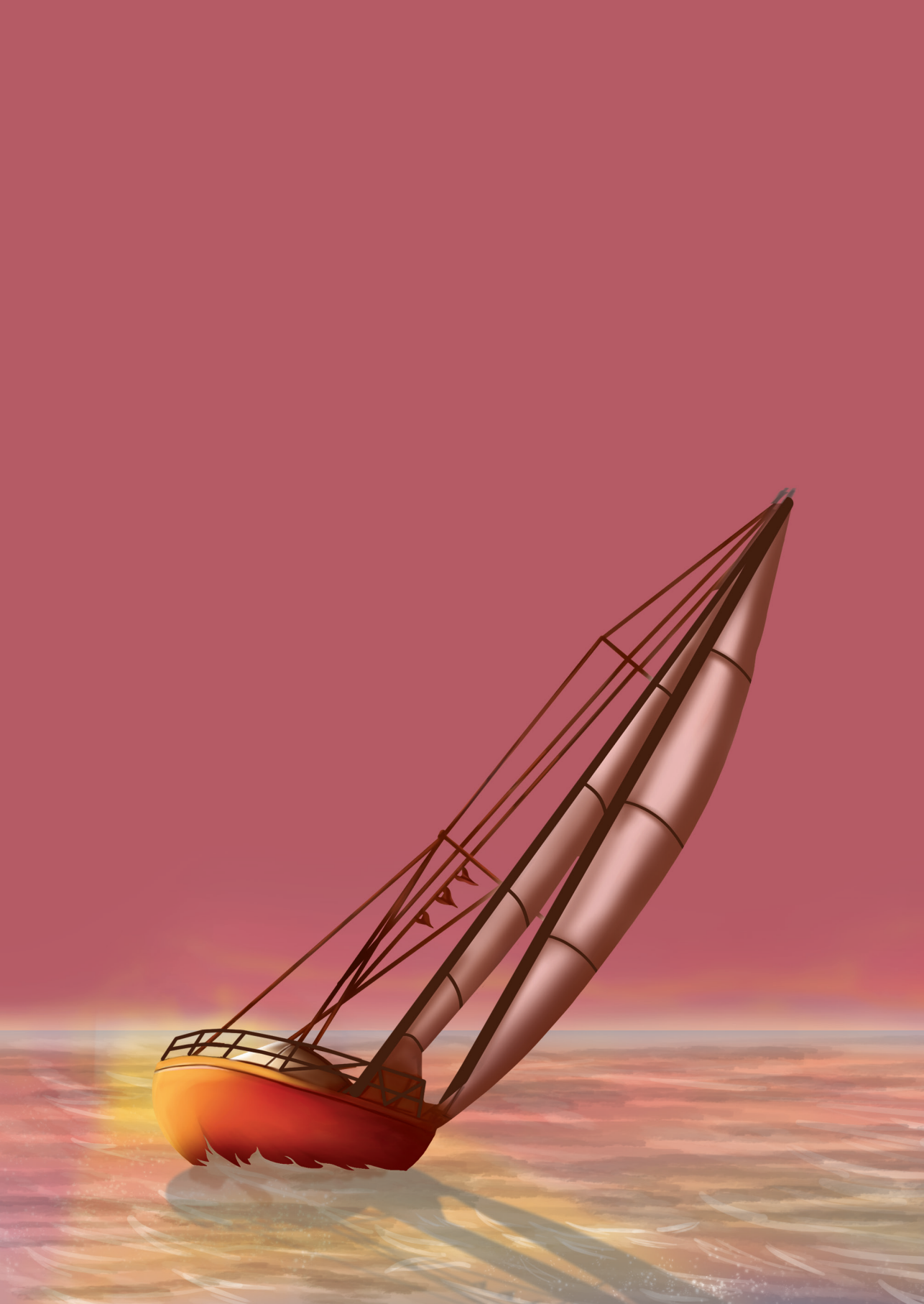
PREMEDICATION USE DURING INSURE AND LISA



CHAPTER 2

SEDATION OF NEWBORN INFANTS FOR THE INSURE PROCEDURE, ARE WE SURE?

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Sinno H.P. Simons

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ABSTRACT

Background: Neonatal intubation is a stressful procedure that requires premedication to improve intubation conditions and reduce stress and adverse physiological responses. Premedication used during the INSURE (INtubation, SURfactant therapy, Extubation) procedure should have a very short duration of action with restoration of spontaneous breathing within a few minutes.

Aims: To determine the best sedative for intubation during the INSURE procedure by systematic review of the literature.

Methods: We reviewed all relevant studies reporting on premedication, distress, and time to restoration of spontaneous breathing during the INSURE procedure.

Results: This review included 12 studies: two relatively small studies explicitly evaluated the effect of premedication (propofol and remifentanil) during the INSURE procedure, both showing good intubation conditions and an average extubation time of about 20 minutes. Ten studies reporting on fentanyl or morphine provided insufficient information about these items.

Conclusions: Too little is known in the literature to draw a solid conclusion on which premedication could be best used during the INSURE procedure. Both remifentanil and propofol are suitable candidates but dose-finding studies to detect effective nontoxic doses in newborns with different gestational ages are necessary.

INTRODUCTION

Endotracheal intubation is a frequently performed procedure in the neonatal intensive care unit (NICU).[1] It is a stressful procedure associated with pain and adverse physiological responses when the neonate is awake. Adverse effects include hypoxia, bradycardia, systemic hypertension, and increased intracranial pressure with a potential risk of intraventricular hemorrhage, especially in preterm infants.[2-6] Intubation without the use of premedication may lengthen the procedure, require a greater number of attempts,[4-6] and cause traumatic damage to the face, eyes, tongue, gums, and glottic structures.[6,7] With this in mind, clinicians have started to routinely administer premedication.[2-4,8-11] However, there is still no consensus about the best drugs for neonatal intubations.[12,13]

The most frequent reason for intubation in preterm neonates is surfactant replacement therapy for respiratory distress syndrome (RDS). Incidence of RDS is 92% in 24-25 weeks, 88% in 26-27 weeks, 76% in 28-29 weeks, and 57% in 30-31 weeks. Starting early with nasal continuous positive airway pressure (nCPAP) can reduce the need for surfactant replacement therapy in RDS by 50%.[14] Historically, surfactant was administered via a tracheal tube during mechanical ventilation. As mechanical ventilation may damage the pulmonary system and cause bronchopulmonary dysplasia (BPD), new techniques have been introduced to shorten the duration of mechanical ventilation as much as possible. In the INSURE (INtubation, SURfactant administration, immediate Extubation) method, infants are endotracheally intubated only for surfactant administration and are extubated immediately thereafter and put on nCPAP again. A Cochrane review in 2008 showed that the INSURE method significantly decreased the need for mechanical ventilation (relative risk (RR) 0.72, 95% confidence interval (CI) 0.59– 0.87), the incidence of BPD (RR 0.68, 95% CI 0.57–0.79) and the incidence of air leak syndromes (RR 0.52, 95% CI 0.28– 0.96).[15]

Intubation in the context of the INSURE procedure still requires the administration of premedication. However, rapid recovery of the respiratory drive is essential for the success of the INSURE procedure. As extubation should take place within several minutes after surfactant administration, the sedative agent used must have a very short duration of action. There is no consensus about what agent is most suitable as premedication for INSURE procedures. The goal of this paper is to determine the most appropriate sedative for neonatal intubation during the INSURE procedure by reviewing the literature.

METHODS

Literature searches in Pubmed and EMBASE were performed to obtain all publications evaluating the effect of premedication for intubation during the INSURE procedure. We searched for information about the intubation conditions, the number of attempts needed for successful intubation, and mainly the time to awakening and extubation. The initial search strategy involved the following keywords: "intubation, intratracheal" (MeSH), "premedication" (MeSH), and "INSURE", with the limit newborn: birth-1 month. This search strategy revealed only two relevant publications.

Therefore we performed an additional search strategy for all publications describing the INSURE procedure and screened these publications for the following information: premedication used, dose of premedication, intubation conditions, number of attempts needed for successful intubation, time to restoration of sufficient breathing pattern, time to extubation, time to start nasal respiratory support, INSURE failure, intractable apnea as a reason for INSURE failure, and time window between extubation and INSURE failure. This search strategy involved the following keywords: "pulmonary surfactants" [MeSH], "respiratory distress syndrome, newborn" [MeSH], "positive pressure respiration" [MeSH], "continuous positive airway pressure" [MeSH], "infant, newborn" [MeSH], and "INSURE" in different combinations. Because the first publication describing the INSURE procedure appeared in 1990, publications in the time frame between January 1990 and June 2013 were sought. Because reviews describing the INSURE procedure do not usually provide any new data about premedication and its effects, we excluded reviews. Reference lists of publications describing the INSURE procedure were screened for other useful publications. Publications in English, Dutch, French, and German were included. The full text of each report describing the INSURE procedure was screened for the abovementioned information.

RESULTS

The overall literature search yielded 12 studies suitable for our review. Only 2 publications, both by Welzing et al., explicitly evaluated the effect of premedication for intubation during the INSURE procedure, that is, remifentanil and propofol, respectively.[16,17] The search strategy for publications describing the INSURE procedure revealed 36 publications.

We excluded 24 studies, 5 because they were written in another language (Danish, Swedish, and Chinese), 2 because any premedication before intubation clearly was not given, and 17 because they did not provide any information about the premedication

used. Thus, ten additional publications were included, next to both studies of Welzing et al. The following sedatives were evaluated: remifentanil, propofol, fentanyl, morphine, and a combination of morphine and pentobarbital. Characteristics of the studies regarding the INSURE procedure are summarized in Table 1 and detailed information about the effects and side effects of the premedication that was used is provided in Table 2.

Remifentanil. In the study of Welzing et al. a total of 21 preterm infants received 10 µg/kg atropine and 2 µg/kg remifentanil prior to intubation. Fifteen patients (71%) were intubated at the first attempt and six patients (29%) at the second attempt. First failed attempts were ascribed to inexperience of residents in training and not to insufficient sedation. Intubation conditions were excellent in 14 patients (67%) and good in 7 patients (33%). No serious side effects occurred. CPAP could be started at a mean of 10.9 minutes (range 1–30 minutes) after surfactant administration, and mean time to extubation was 42.4 minutes (range 1–330 minutes).[16]

Propofol. A pilot study of Welzing et al. evaluated the effect of propofol as premedication before intubation during the INSURE procedure. This pilot was supposed to continue for one year but was stopped prematurely because of significant problems with arterial hypotension. Thirteen preterm infants underwent the INSURE procedure and received 10 µg/kg atropine and 1 mg/kg propofol. Intubation was successful at the first attempt in nine patients (69%) and at the second attempt in four patients (31%). Failed first attempts were ascribed to inexperience of residents in training. Intubation conditions were excellent in five, good in six, and inadequate in two patients, respectively. Propofol gave only a short period of respiratory depression and nCPAP could be started at a mean of 25 minutes (2 to 120 minutes) after surfactant administration. One patient needed reintubation after INSURE because of inadequate respiratory drive. In 5 of 13 patients significant arterial hypotension was observed.[17]

Morphine. Five of the 10 additionally included publications concerned morphine monotherapy in a dosage of 100 or 200 µg/kg.[18-22] The use of naloxone was optional in most studies,[18,19,21] standard practice in one study,[22] and not mentioned in one study.[20] None of these five studies provided details on intubation conditions and number of attempts for successful intubation. The studies of Van den Berg et al. and Flor-de-Lima et al. did not address time to restoration of spontaneous breathing and INSURE failure because of insufficient breathing or apnea.[18,22] In the study of Cherif et al., all patients were extubated within 6.3 ± 1.7 minutes (range 5–12 minutes) after surfactant administration. However, INSURE failed in 35 patients (32.1%) but reasons for this failure and the time frame between extubation and INSURE failure were not mentioned.[20] Verder et al. did not mention time to extubation but did mention INSURE failure in 15 patients (43%): 2 patients

Table 1. Characteristics of included studies

Author	Kind of study	Inclusion criteria INSURE	Exclusion criteria INSURE
Ancora et al.[26]	Retrospective case control study	FiO_2 requirement >0.40 on nCPAP >30 min to maintain SpO_2 values 85-95% in presence of radiological signs of RDS	Not reported
Van den Berg et al.[22]	Prospective cohort study	Not reported	Not reported
Bohlin et al.[23]	Retrospective descriptive study	Preterm with RDS on nCPAP with a/A ratio ≤0.22	Infants requiring intubation as part of resuscitation at birth
Cherif et al.[20]	Retrospective case study	GA >27 weeks, a/A ratio ≤0.25 on nCPAP	Not reported
Gizzi et al.[25]	Retrospective case study	FiO_2 requirement >0.40 on nCPAP >30 min to maintain SpO^2 values 85-93% in the presence of radiologic signs of RDS	Not reported
Flor-de-Lima et al.[18]	Retrospective case control study	FiO_2 >0.40 with respiratory distress and/or arterial pCO_2 >65 mmHg and pH <7.0 on nCPAP	Not reported
Leone et al.[27]	Case control study	Preterm with RDS on nCPAP with a/A ratio ≤0.22	Infants requiring intubation as part of resuscitation at birth or later as part of respiratory failure
Sandri et al.[24]	RCT	GA 28-32 weeks, inborn, FiO_2 on nCPAP >0.40 for >30 min to maintain SpO_2 93-96% and radiographic signs of RDS	

Definition of intubation conditions	Definition of INSURE failure	Predefined side effects
Not defined	FiO_2 > 0.40 on nCPAP, intractable apnea (>4 episodes of apnea/hour or >2 episodes of apnea/hour requiring bag and mask ventilation) or severe respiratory acidosis (pH <7.12 and pCO_2 >70 mmHg) within 7 days from extubation	Not defined
Not defined	Not defined	Not defined
Not defined	Need for MV in first week after surfactant treatment. Need for MV: $PaCO_2$ ≥8.5 kPa, FiO_2 ≥0.60, signs of severe respiratory distress or apnea	Not defined
Not defined	Need for MV during 24 hours after surfactant treatment. Criteria for MV: >3 episodes of apnea per 3 hours irresponsive of stimulation and caffeine treatment, arterial pH <7.20, arterial pCO_2 >65 mmHg, a/ApO_2 <0.15, metabolic acidosis not responsive to treatment	Not defined
Not defined	FiO_2 >0.40 to maintain SpO_2 85-95%, significant apnea defined as >4 episodes of apnea/hour or >2 apnea/hour requiring bag and mask ventilation, respiratory acidosis pCO_2 >65 mmHg and pH <7.20)	Not reported
Not defined	Not defined	Not defined
	Need for MV during admission to the NICU. Criteria for MV: $PaCO_2$ ≥8.5 kPa, FiO_2 ≥0.60, signs of severe respiratory distress or apnea	
	Need for MV during first week. Criteria: FiO_2 >0.40 for SpO_2 85-93%, significant apnea (>4 apnea/hour or >2 apnea/hour requiring bag and mask ventilation), respiratory acidosis (pCO_2 >65 mmHg, pH <7.20), FiO_2 rapidly increasing >0.80	

Table 1. Characteristics of included studies - continued

Author	Kind of study	Inclusion criteria INSURE	Exclusion criteria INSURE
Verder et al. 1994[19]	RCT	GA 25-35 weeks, clinical and radiologic signs of RDS, PNA 2-72 hours, nCPAP with PEEP ≥6 cm H_2O, a/A ratio ≤0.22	AS <3 at 5 min, PPROM >4 days, severe malformations, pneumonia, pneumothorax
Verder et al.1999[21]	RCT	GA <30 weeks, PNA 2-72 hours, nCPAP with PEEP ≥6 cm H_2O for RDS, a/A ratio 0.35-0.22 decreasing over a period of >30 min	AS ≤2 at 5 min, PPROM >3 weeks, lethal malformations, pneumonia, incompletely treated pneumothorax
Welzing et al.2010[17]	Prospective cohort study	GA 29-32 weeks, PNA <8 hours, moderate to severe respiratory distress (FiO_2 ≥0.30 on nCPAP for SpO_2 ≥88% or Silverman score ≥6)	Any kind of disease not allowing early extubation
Welzing et al. 2009[16]	Prospective cohort study	GA 29-32 weeks, PNA <8 hours, moderate to severe respiratory distress (FiO_2 ≥0.30 on nCPAP for SpO_2 ≥88% or Silverman score ≥6)	Any kind of disease not allowing early extubation

Abbreviations: AS, Apgar score; GA, gestational age; MV, mechanical ventilation; nCPAP, nasal continuous positive airway pressure; PEEP, positive end-expiratory pressure; PNA, postnatal age; PPROM, preterm premature rupture of membranes; RDS, respiratory distress syndrome.

could not be extubated after surfactant administration and another 13 patients had to be reintubated. In 10 of these 15 patients the reason for INSURE failure was recurrent apnea. Information regarding the time frame between extubation and INSURE failure was lacking.[19] In another study Verder et al. found that four patients (7%) could not be extubated after surfactant administration. In two patients the reason was intractable apnea, which is a side effect of morphine. In this study the use of morphine was optional and the authors did not mention if these two patients had received morphine.[21]

In the study of Bohlin et al., patients received a combination of 200 µg/kg morphine and 2 mg/kg pentobarbital prior to intubation. Naloxone 100 µg/kg was administered to all patients before extubation. Information regarding intubation conditions, number

	Definition of intubation conditions	Definition of INSURE failure	Predefined side effects
	Not defined	Not defined	Not defined
	Not defined	Need for MV within 7 days of birth. Criteria for MV: a/A values <0.15 decreasing further over a period >30 min, severe apnea (>4 episodes of apnea/hour or need for bag and mask ventilation >2 times per hour), inability to extubate within 1 hour after INSURE	Not defined
	Score 0-2 on coughing, breathing, and limb movements (≤1 = excellent, 2-3 = good, >3 or distinct coughing or limb movement = inacceptable)	Not reported	Hypotension
	Score 0-2 on coughing, breathing, and limb movements (≤1 = excellent, 2-3 = good, >3 or distinct coughing or limb movement = inacceptable)	Not reported	Hypotension, bradycardia, chest rigidity

of attempts, and extubation time was not provided. Eight patients (19%) could not be extubated after surfactant administration. This was related to the premedication in only one patient, who received an overdose of pentobarbital.[23]

Fentanyl. Four studies used fentanyl as premedication; two studies at a dose of 0.5–2 µg/kg,[24,25] one study at a dose of 1–3 µg/kg,[26] and one study at a dose of 0.2 mg/kg.[27] None of these four studies detailed the intubation conditions, number of intubation attempts, and time to return of spontaneous breathing and extubation. The studies of Sandri et al. and Leone et al. also provided no information about INSURE failure.[24,27] In the study of Gizzi et al. INSURE failed in 11 patients (35%) who were extubated to nasal CPAP. In four patients the reason for INSURE failure was intractable apnea and the time frame between surfactant administration and INSURE failure was 48.1 hours (range 5 - 72 hours).

Table 2. Summary of premedication used before intubation in publications studying the INSURE procedure

Author	Premedication and dosage	Number of patients
Ancora et al.[26]	Atropine 20 µg/kg, fentanyl 1-3 µg/kg, naloxone 40 µg/kg optional	38
Van den Berg et al.[22]	Morphine 100 µg/kg or pethidine 1 mg/kg, naloxone 10 µg/kg before extubation	16
Bohlin et al.[23]	Morphine 200 µg/kg and pentobarbital 2 mg/kg, naloxone 0.1 mg/kg before extubation	42
Cherif et al.[20]	Morphine 200 µg/kg	109
Flor-de-Lima et al.[18]	Morphine 100 µg/kg, naloxone 100 µg/kg optional	15
Gizzi et al.[25]	Fentanyl 0.5-2 µg/kg, naloxone 40 µg/kg optional	64
Leone et al.[27]	Fentanyl 0.2 mg/kg	42
Sandri et al.[24]	Fentanyl 0.5-2 µg/kg	51
Verder et al. 1994[19]	Morphine 100 µg/kg, atropine 10 µg/kg, naloxone 10 µg/kg optional	35
Verder et al.1999[21]	Morphine 100 µg/kg, atropine 10 µg/kg, naloxone 10 µg/kg optional	60
Welzing et al. 2009[16]	Remifentanil 2 µg/kg and atropine 10 µg/kg	21
Welzing et al. 2010[17]	Propofol 1 mg/kg and atropine 10 µg/kg	13

Abbreviations: BW, birth weight; GA, gestational age; CPAP, nasal continuous positive airway pressure.

In patients who were extubated to nasal intermittent positive pressure ventilation (nIPPV), INSURE failed in two patients (6%) on account of increased oxygen requirement.[25] Ancora et al. reported INSURE failure in 14 patients (37%), on account of insufficient respiratory drive in 13 patients. INSURE failure occurred at a mean of 99 hours (range 1–150 hours) after extubation.[26] None of the studies reported the necessity of naloxone therapy after fentanyl.

Patient characteristics	Time to extubation	INSURE failure	Reasons for INSURE failure
GA < 32 weeks and BW <1500 grams	Not described	14 patients	Severe apnea in 13 patients
GA < 32 weeks	Not described	Not described	Not described
GA 27-34 weeks	Not described	1 patient	Overdose of pentobarbital
GA 27-35 weeks	6.3 ± 1.7 min (range 5-12 min)	35 patients	Not described
BW < 1500 grams	Not described	Not described	Not described
GA < 32 weeks	Not described	13 patients	Apnea in 4 patients
GA < 34 weeks	Not described	Not described	Not described
GA 28-32 weeks	Not described	Not described	Not described
GA 25-35 weeks	Not described	15 patients	Apnea in 10 patients
GA < 30 weeks	Not described	4 patients	Apnea in 2 patients
GA 29-32 weeks	Start CPAP at 10.9 min (1-30 min) and extubation at 42.4 min (1-330 min)	Not described	Not described
GA 29-32 weeks	Start CPAP at 25 min (2-120 min)	1 patient	Inadequate respiratory drive

DISCUSSION

Although the need for premedication before neonatal intubation is well recognized, there is no consensus on the most effective sedative to eliminate pain, discomfort, and physiological instability and to provide conditions for a rapid and safe intubation without adverse effects. Moreover, duration of action must be as short as possible to allow for a sufficient breathing pattern within several minutes after surfactant administration, so that extubation can be performed as quickly as possible (see Figure 1). This review found that only two pharmacological studies evaluated the effect of premedication for the INSURE procedure, that is, remifentanil and propofol.

Remifentanil, a synthetic opioid, was introduced into clinical practice in 1996 and is therefore the newest opioid available.[28,29] Because of hydrolysis by nonspecific tissue and plasma esterases, metabolism is not dependent on liver and renal function, and it is also not age related.[30-34] Metabolism produces a metabolite known as remifentanil acid, which has no clinical significant activity.[29,31,32] This unique pharmacokinetic profile provides ultrashort action, high predictability, rapid onset and offset of action, immediate recovery of the clinical effect after interruption of the administration, a short context-sensitive half-life and short elimination time not influenced by the infusion time, and no accumulation of the drug.[30,31] These positive effects of remifentanil were evident in several reviewed studies.[32-39]

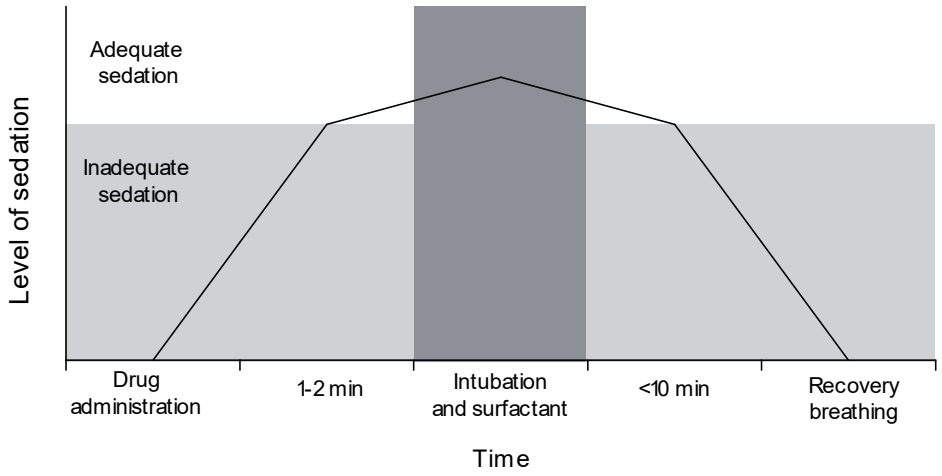

Figure 1. Ideal sedation model for the INSURE procedure

Choong et al. investigated the effect of remifentanil as premedication in neonatal elective intubations. They found good intubation conditions (using a seven-point Likert scale) and few intubation attempts were needed. Mean time to return of spontaneous respiration in those patients who did not receive any additional drugs besides remifentanil was 210 seconds.[30] This finding supports our hypothesis that remifentanil is suitable for the INSURE procedure. In the study of Welzing et al. remifentanil was also found to be effective for neonatal intubation. Intubation conditions were good or excellent in all patients and the vast majority of patients were intubated at the first attempt.[16] However, the authors' conclusions about the very short period of respiratory depression and early reinstitution of CPAP after surfactant treatment are debatable. The time to extubation was rather long (42.4 minutes and still 16.9 minutes after excluding 3 patients on prolonged endotracheal CPAP for logistic reasons) and does not perfectly meet the criterion of

immediate extubation. To our opinion it therefore feels somewhat preliminary to state that remifentanil is an appropriate sedative to use as premedication for neonatal intubation during the INSURE procedure. Reduced clearance of remifentanil in the first postnatal days could probably explain the prolonged effect, and it would seem desirable to evaluate lower remifentanil doses that have not yet been studied. More research with remifentanil during the INSURE procedure in a larger group of preterm infants of variable gestational ages is needed.

Propofol is a short acting anesthetic that is rapid in onset and short in duration and can preserve spontaneous respirations.[40] It is a highly lipophilic compound and exhibits rapid distribution from blood into subcutaneous fat and the central nervous system with subsequent redistribution. Propofol clearance mainly depends on hepatic blood flow with subsequent metabolism. Although multiple hepatic and extrahepatic human cytochrome p450 isoforms are involved in propofol metabolism, glucuronidation is the major metabolic pathway.[41] A study of Ghanta et al. found that, with the use of propofol 2.5 mg/kg, successful intubation was reached twice as fast as with the combination of morphine, atropine and suxamethonium, fewer attempts were needed, and patients regained spontaneous movements twice as fast.[12]

Nevertheless, several studies have shown reduced propofol clearance notably in preterm neonates and neonates in the first 10 days of life, leading to accumulation of the drug during continuous infusion and bolus administration. Preterm neonates and neonates in the first 10 days of life are even more prone to display reduced clearance. After correcting for postmenstrual age and postnatal age, there is still extensive unexplained interindividual variability in propofol clearance in neonates, making prediction in neonates more difficult.[40-43]

Welzing et al. evaluated the effect of propofol in a dose of 1 mg/kg in 13 patients undergoing INSURE. Propofol seemed to be very suitable and provided excellent or good intubation conditions in most patients and a very short period of respiratory depression.[17] We feel, however, that the 25 minutes' time to extubation is too long. Also, one patient needed reintubation because of insufficient breathing. Again, the rather long time to extubation may be explained perhaps by reduced clearance of propofol in preterm infants in the first 10 days of life which leads to longer duration of the sedative effect. Dose-finding studies in preterm infants of different gestational and postnatal ages should be performed to determine the appropriate dose of propofol for different gestational and postnatal ages.

Further concerns about propofol in preterm neonates include the relatively high incidence of side effects, especially profound hypotension. The pilot study of Welzing et al. was stopped prematurely because of significant hypotension in five patients.[17] The relatively long-lasting sedation and high incidence of hypotension point at excessive propofol doses. Evidence on the hypotensive side effect of propofol is not consistent: some studies report relatively high frequencies of hypotension,[40,44-46] but this is not confirmed by others.[12,31,47] Vanderhaegen et al. studied the cerebral and systemic hemodynamic effects of propofol in neonates and found a short lasting decrease in cerebral oxygenation of several minutes and a decrease in mean arterial blood pressure up to 1 hour after propofol administration.[40] Possible age-related propofol dose response of neonates needs further exploration. The adequate propofol doses that provide good sedation, no hypotension or decreased cerebral perfusion, and fast restoration of sufficient breathing have yet to be found. Also, more research into the adequate doses of propofol for different gestational age groups during the INSURE procedure is needed. Once known, propofol should be compared with remifentanil in a randomized controlled manner, to evaluate which drug would be best with the fewest side effects.

Of all other 10 publications describing the INSURE procedure, only the one by Cherif et al. on morphine reported a time to extubation, that is 6.3 ± 1.7 minutes (range 5–12 minutes).[20] Based on the PK/PD profile of morphine in newborns this seems to be quite short and morphine might not even have reached maximum concentration, also in view of the fact that INSURE failed in 32% of patients. This may have been due to recurrent apnea due to opioid induced respiratory depression. All other nine studies did not mention time to awakening and extubation but some of the studies mentioned INSURE failure because of intractable apneas.[19,21,23,24,26] Opioid induced respiratory depression probably was the cause of these apneas.

Morphine has several limitations, notably delayed onset and prolonged duration of action, on account of which it is unsuitable to be used as a sedative in neonatal intubation.[6,11,36] This is confirmed by several studies. Lemyre et al. performed a randomized placebo controlled trial of morphine and found no differences between morphine and placebo in duration of distortion of vital parameters, duration of the intubation procedure, and number of attempts.[48] Several other studies compared morphine with other premedication regimens and unanimously found that morphine was less effective, providing worse intubation conditions and necessitating a greater number of attempts.[12,36,49] The prolonged duration of action of morphine could be antagonized with naloxone. However, naloxone also antagonizes endorphins and results in a direct very distressful condition and has the potential to cause cardiac arrest, as reported in an extremely preterm infant and two adult patients.[50] Also, the duration of action of naloxone is much shorter than that of morphine.

Therefore, opioid induced respiratory depression antagonized with naloxone can easily return after the effect of naloxone has worn off. All this makes clear that morphine should not be used as premedication in neonatal intubation, especially during the INSURE procedure. Short acting opioids therefore probably are more suitable.

Other short acting drugs or combinations of drugs that could theoretically be used as rapid sequence induction for the INSURE procedure, such as midazolam or remifentanil combined with propofol or with thiopental, have not been reported in the literature yet.[49]

CONCLUSION

In conclusion, propofol and remifentanil both have a very short onset and duration of action and are in theory the most suitable candidates for INSURE procedure premedication. However, only two relatively small studies have evaluated the effects of propofol and remifentanil in this context and insufficient data are available about optimal dosing, effects, and side effects. Therefore, more research including dose-finding studies and randomized controlled trials that compare different drugs are necessary. Morphine should be considered unsuitable because of its delayed onset and prolonged period of action. This literature review revealed too little information to draw a solid conclusion.

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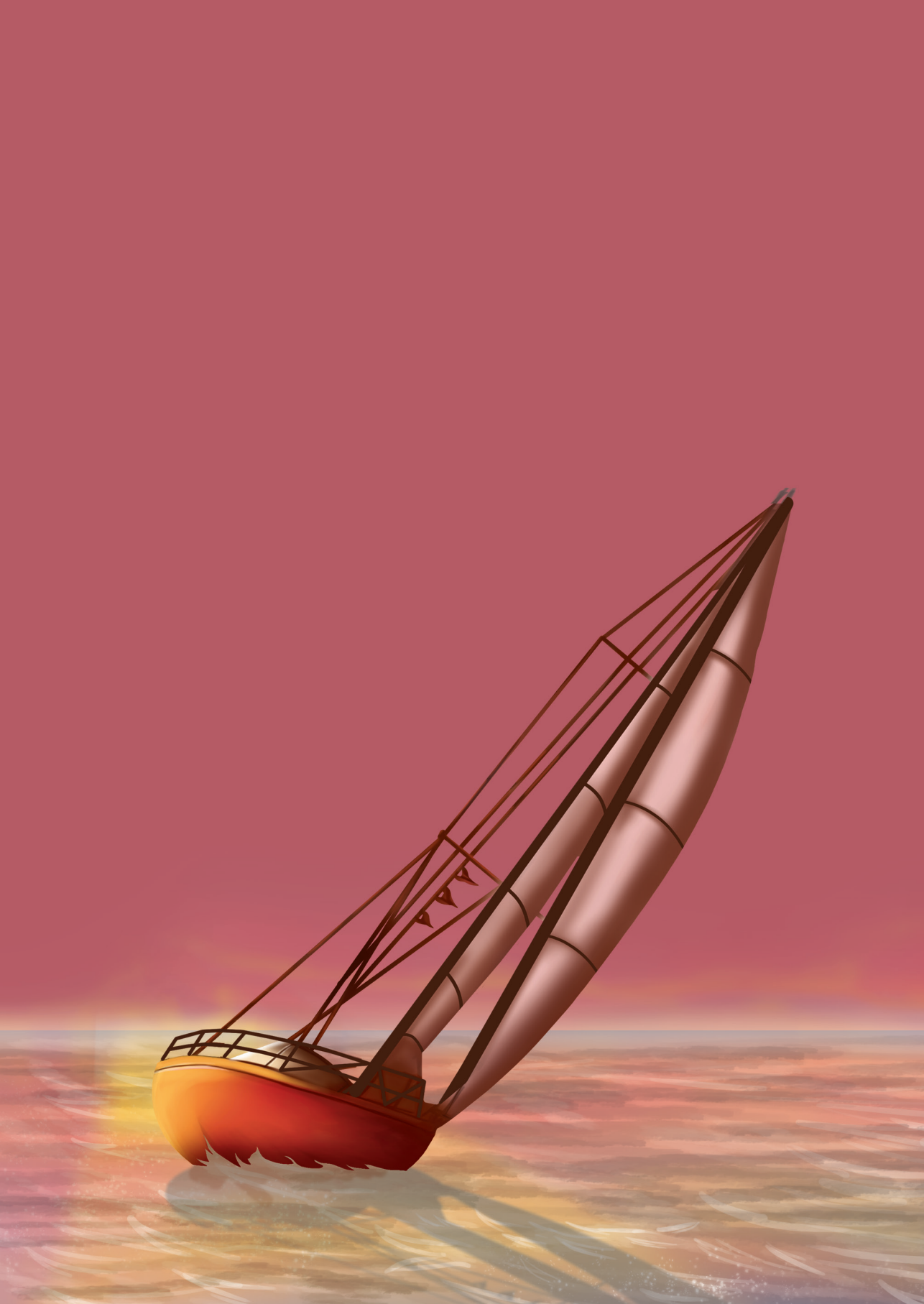

CHAPTER 3

INSUFFICIENT SEDATION AND SEVERE SIDE EFFECTS AFTER FAST ADMINISTRATION OF REMIFENTANIL DURING INSURE IN PRETERM NEWBORNS

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ABSTRACT

Background: Neonatal intubation is stressful and should be performed with premedication. In the case of an INSURE (intubation/surfactant/extubation) procedure a short duration of action of the premedication used is needed to facilitate fast extubation. Given its pharmacological profile, remifentanil seems a suitable candidate.

Objectives: The aim here was to evaluate the effect and side effects of remifentanil as premedication for preterm neonates undergoing INSURE.

Methods: A prospective, single center study in a level III neonatal intensive care unit was conducted. The quality of sedation was assessed in preterm infants receiving remifentanil prior to intubation for the INSURE procedure. Intravenous remifentanil was administered quickly and followed by a saline flush in approximately 30 s. The quality of sedation was defined by a combination of adequate sedation score, good intubation conditions and absence of side effects.

Results: The study was terminated after the inclusion of 14 patients because of the high rate of side effects and the poor intubation conditions. Adequate sedation was achieved in only two patients (14%). Six patients (43%) needed additional propofol to obtain adequate sedation. Chest wall rigidity occurred in six patients (43%).

Conclusions: The rapid administration of remifentanil provides insufficient sedation and is associated with a high risk of chest wall rigidity in preterm neonates.

INTRODUCTION

To prevent distress and adverse physiological responses, traumatic damage and failed procedures, neonatal intubation should always be performed with the use of premedication.[1-3] One of the most frequent reasons to intubate neonates is to administer surfactant for respiratory distress syndrome. During the INSURE (intubation, surfactant, extubation) procedure, patients are only briefly intubated for the administration of surfactant and extubated immediately thereafter. To facilitate this rapid extubation, the premedication used should have a rapid onset and very short duration of action.

A recent review on the use of premedication before intubation during the INSURE procedure showed no conclusive evidence on the optimal premedication but stated that remifentanil was probably the best candidate because of its unique pharmacological profile.[4] Remifentanil has an extremely brief action, high predictability, rapid onset and offset of action, and immediate recovery of the clinical effect after interruption of the administration.[5] The results of previous studies using remifentanil as single agent were also encouraging.[6-8] We performed an observational prospective study to evaluate the effects and side effects of remifentanil bolus infusion as premedication before the INSURE procedure and report here the results of implementing remifentanil into clinical practice.

METHODS

Study population

This prospective study was performed at the level III neonatal intensive care unit of the Erasmus MC Sophia Children's Hospital in Rotterdam, the Netherlands. Before January 2013, surfactant was always administered during a period of mechanical ventilation and propofol was used as premedication before intubation. In January 2013 the standard of care was changed to performing the INSURE procedure for the administration of surfactant in all infants with a gestational age ≥27 weeks and birth weight ≥750 g. As premedication for the INSURE procedure we started to use remifentanil. Remifentanil was administered intravenously as a fast bolus and followed by an intravenous saline flush in 30 s. After administration, the level of sedation was assessed with a standardized sedation score, performed by rubbing the sole of the patient's foot and judging the motor reaction to that stimulus (1 = spontaneous movement; 2 = movement on slight touch; 3 = movement in reaction to firm stimulus; 4 = no movement).[9] In case of inadequate sedation (score 1 or 2), another dose of remifentanil was administered according to the protocol. If sedation was adequate (score 3 or 4), the procedure was

continued. INSURE procedures were always performed by neonatologists and clinical fellows experienced in neonatal intubations. As soon as the respiratory drive recovered after surfactant administration, the patient was extubated and commenced with nasal continuous positive airway pressure.

Use of remifentanil

Based on the results of the study by Avino et al.[7] and our inexperience with remifentanil, we decided to start with a low dose of 1 µg/kg. When sedation was inadequate, this dose could be repeated no more than twice (period 1). If sedation was still inadequate after three doses, the patient received propofol (1 mg/kg) and surfactant was administered in the conventional way. Because sedation was inadequate in four of the first five patients, the starting dose of remifentanil was increased to 2 µg/kg. When sedation was inadequate, another dose of remifentanil was given and each subsequent dose was increased with 1 µg/kg relative to the previous dose with a maximum dose of 5 µg/kg (period 2). If sedation was still insufficient, propofol (1 mg/kg) was given and surfactant was administered in the conventional way.

Outcome measures

The primary outcome measure was the quality of sedation, defined as the combination of an adequate sedation score, adequate intubation conditions and the absence of side effects. Intubation conditions were classified with a validated intubation score by rating laryngoscopy, vocal cords, coughing, jaw relaxation and limb movements (Table 1).[10] Intubation conditions were good when the total score was ≤10 with a score on each item ≤2. Hypotension and chest wall rigidity were defined as side effects. Hypotension was defined as a mean blood pressure lower than gestational age and chest wall rigidity was defined as the inability to inflate with normal pressures. Secondary outcomes were the number of remifentanil doses, maximum remifentanil dose, need for propofol to achieve adequate sedation and intubation attempts.

Table 1. Intubation score

Item	Score 1	Score 2	Score 3	Score 4
Laryngoscopy	Easy	Fair	Difficult	Impossible
Vocal cords	Open	Moving	Closing	Closed
Coughing	None	Slight	Moderate	Severe
Jaw relaxation	Complete	Slight	Stiff	Rigid
Limb movements	None	Slight	Moderate	Severe

Ethics committee approval

We received a waiver for ethical approval of the observational trial according to the Dutch Law of Research with Humans (No. 2014.435; Medical Ethical Committee, Erasmus Medical Center, Rotterdam, the Netherlands).

RESULTS

Characteristics of included patients

Due to insufficient sedation and a high rate of side effects, the use of remifentanil was terminated after the inclusion of 14 patients: 5 patients in study period 1 and 9 patients in study period 2. The baseline characteristics of the study patients and outcomes in study period 1 and study period 2 are reported in Table 2.

Primary outcome measures

Adequate sedation was by the combination of three key components: adequate sedation score, adequate intubation conditions and the absence of side effects. This was achieved in only two patients (14%) of our total study population. In study period 1, two patients had an adequate sedation score but one of them had inadequate intubation conditions despite this score. In the remaining three patients the sedation score was inadequate. Two of them were intubated with propofol while the other was intubated despite the inadequate sedation score. None of the patients developed chest wall rigidity. In summary, adequate sedation based on the three key components was only achieved in one patient in study period 1. In study period 2 adequate sedation scores after remifentanil were achieved in six patients. However, only one patient also had adequate intubation conditions and no side effects. One patient had inadequate intubation conditions and four patients developed chest wall rigidity. In two of these latter patients, intubation failed or was never tried and propofol was administered. The sedation score was inadequate in three patients. In two of these patients propofol was used and one patient was intubated despite an inadequate sedation score. Two of these three patients developed chest wall rigidity. In summary, in study period 2 adequate sedation based on the three key components was also only achieved in one patient.

Chest wall rigidity was a frequently reported side effect, occurring in six patients (43%), all in study period 2 (67% of patients in study period 2). Chest wall rigidity always occurred directly after the administration of remifentanil and never after the administration of propofol. No other side effects such as hypotension were identified.

Table 2. Patient characteristics and study outcomes in study periods 1 and 2

	Study period 1 n = 5	Study period 2 n = 9
Patient characteristics		
Gestational age (weeks), median (range)	29 2/7 (28 0/7 to 35 0/7)	28 3/7 (27 3/7 to 32 0/7)
Birth weight (g), median (range)	1,320 (920 – 2,200)	1,130 (910 – 1,860)
Gender	1 male, 4 females	4 males, 5 females
Primary outcome measures – sedation parameters with remifentanil		
Adequate sedation score (3 or 4)	2 (40)	6 (67)
Adequate intubation score (≤10)	2 (40)	4 (44)
Side effects (chest wall rigidity)	0	6 (67)
Adequate sedation	1 (20)	1 (11)
Secondary outcome measures		
Doses of remifentanil		
1	1 (20)	2 (22)
2	2 (40)	5 (56)
3	1 (20)	1 (11)
4	1 (20)	1 (11)
Propofol needed	2 (40)	4 (44)
Intubation attempts		
1	2 (40)	5 (56)
2	2 (40)	3 (33)
3	1 (20)	0
Not reported	0	1 (11)

Outcome measures are presented as patients, n (%) unless otherwise indicated.

Secondary Outcome Measures

Overall, six patients (43%) needed propofol to reach adequate sedation. In the eight patients that achieved an adequate sedation score with only remifentanil, three (38%) needed 1 dose, four (50%) received 2 doses and one (12%) received 4 doses. The maximum dose was 1 µg/kg in three patients (38%), 2 µg/kg in two patients (25%) and 3 µg/kg in three patients (38%). Table 2 displays the number of remifentanil doses in both study periods. Overall, intubation was successful at the first attempt in 54% of patients, 38% of patients required a second and 8% a third attempt. Four intubation attempts failed due to inadequate sedation.

DISCUSSION

We aimed to evaluate the effectiveness of remifentanil premedication for the INSURE procedure in preterm neonates. However, the results of our observational study show that low doses (1 µg/kg) did not provide adequate sedation and rapidly administered remifentanil resulted in an unacceptable high incidence of chest wall rigidity following a high dose. Based on these results we conclude that remifentanil bolus infusion in 30 s is not suitable as premedication for neonatal intubation.

Remifentanil as the single premedication drug has been investigated in three previous studies. Welzing et al. studied 2 µg/kg of remifentanil administered over 60 s in preterm infants undergoing the INSURE procedure.[6] A single dose provided adequate sedation in 81% of patients, with 19% needing a second dose and none of the patients requiring additional medication. Intubation was successful at the first attempt in 71% of patients, insufficient sedation was never the reason for a second attempt and intubation conditions were excellent or good in all patients. No chest wall rigidity was reported. Avino et al. administered 1 µg/kg of remifentanil over 60 s to 36 preterm infants needing (semi-) elective intubation and reported similar results to the previous study.[7] Intubation was successful at the first attempt in 75% of patients but poor intubation conditions occurred in 24% of intubation attempts. Chest wall rigidity occurred in two patients (6%). Choong et al. also investigated remifentanil in elective intubation in neonates at a dose of 3 µg/kg administered over 60 s.[8] They found less positive results, with additional medication needed in 26.7% of patients, failed first attempts in 60% of patients, and excellent or good intubation conditions in only 53.6% of patients. Chest wall rigidity was observed in 13% of patients. In our study, remifentanil was found to provide sufficient sedation in only a small number of patients. An explanation may be the faster infusion rate used in our study. Fast infusion is related to higher peak levels, and as a consequence increased side effects and shorter duration of effective sedation.[6,11] The window of opportunity might have been too short to obtain an adequate sedation score and intubation procedure. We also found a significantly higher incidence of chest wall rigidity, most likely also attributable to the faster infusion rate of 30 s. In retrospect, the chosen duration of infusion was too fast in our study. We used an infusion rate of 30 s to flush the small volume of remifentanil because this is the standard way to administer many semi-acute cardiorespiratory drugs in our intensive care. The results of the current study underline the danger of such a routine way to administer drugs. Based on our results, this is obviously not appropriate and represents important knowledge for other clinicians and researchers who intend to use remifentanil in preterm neonates.

Our study has several limitations, including the small number of patients, no control group treated with another sedative such as propofol, no blinding of doses and no pharmacokinetic analyses of remifentanil. However, our results are an important illustration of daily neonatal care. The combination of opioids with a hypnotic or sedative agent might be more appropriate than the use of a single agent. A slower infusion of remifentanil combined with a low dose of propofol might by an interesting combination to investigate in future studies.

CONCLUSIONS

We conclude that remifentanil boluses administered in 30 s carry an unacceptably high risk of chest wall rigidity in preterm neonates. Lower doses also provide insufficient sedation.

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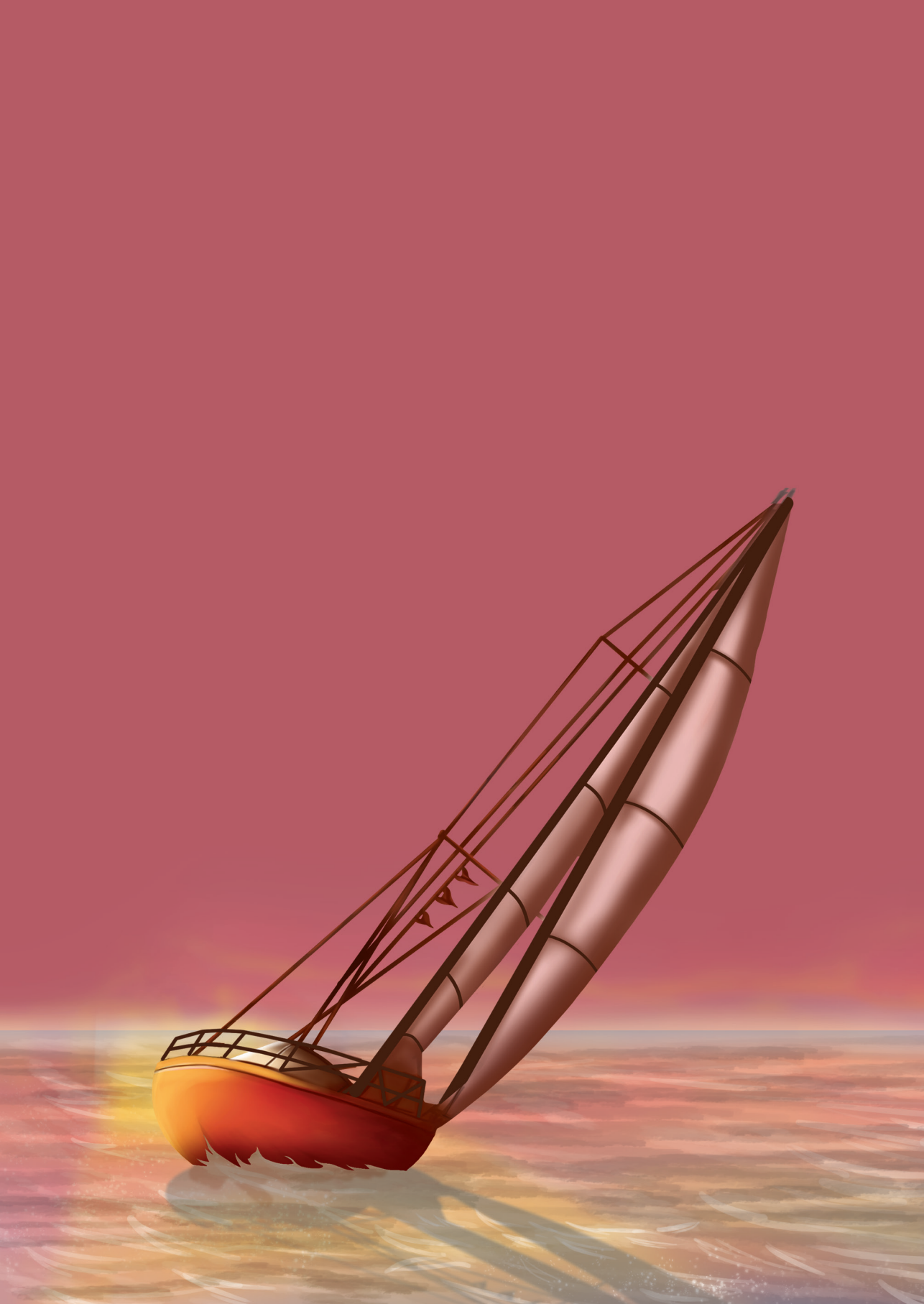

CHAPTER 4

QUALITY ASSESSMENT AND RESPONSE TO LESS INVASIVE SURFACTANT ADMINISTRATION (LISA) WITHOUT SEDATION

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ABSTRACT

Background: Although sedative premedication for endotracheal intubation is considered standard of care, less invasive surfactant administration (LISA) is often performed without sedative premedication. The aim of this study was to assess success rates, technical quality and vital parameters in LISA without sedative premedication.

Methods: Prospective observational study in 86 neonates <32 weeks' gestation. LISA was performed according to a standardized protocol without use of sedative premedication. Outcome measures were success rates of LISA attempts, reasons for failure and quality of technical conditions. In 37 neonates, heart rate and oxygen saturation levels form 20 min before until 30 min after start of LISA were collected.

Results: In 48% of LISAs the first attempt failed and in 41% quality of technical conditions was inadequate. The success rate was significantly correlated with quality of technical conditions and experience of the performer. Desaturations <80% occurred in 54% of patients while bradycardia <80/min did not occur.

Conclusion: This study shows a relatively low success rate of the first attempt of LISA, frequent inadequacy of technical quality and frequent oxygen desaturations. These effects may be improved by the use of sedative premedication.

INTRODUCTION

Respiratory distress syndrome (RDS) is one of the major causes of neonatal respiratory morbidity and mortality.[1] Although the early use of nasal continuous positive airway pressure (CPAP) significantly reduced the need for surfactant replacement therapy in RDS, still over half of all preterm neonates with RDS require surfactant.[2] Historically, surfactant was administered via an endotracheal tube during a period of mechanical ventilation. As mechanical ventilation may cause ventilator-induced lung injury and increases the risk of bronchopulmonary dysplasia (BPD),[3] the technique of less invasive surfactant administration (LISA) was developed. In this technique, surfactant is administered via a thin catheter in spontaneously breathing infants on nasal CPAP.[4] A systematic review including six randomized controlled trials with a total of 895 patients showed a significantly reduced incidence of BPD and death and a lesser need of mechanical ventilation in infants treated with LISA compared to infants treated with surfactant via an endotracheal tube during mechanical ventilation.[5]

From endotracheal intubation studies in neonates it is long known that awake laryngoscopy is distressing and painful, and is frequently complicated by a series of serious adverse physiological events.[6-16] Also, awake intubation increases the time and the number of attempts necessary for successful intubation and increases the risk of traumatic injury to the airway.[12,13,17] Therefore, in a consensus statement on the prevention and management of pain in the newborn in 2001 and again by the American Academy of Pediatrics in 2010, it was stated that nonemergency intubation should always be performed with the use of premedication.[18,19] There is no consensus about the optimal premedication strategy.[19]

Similar to endotracheal intubation, LISA involves the use of a laryngoscope to place the thin catheter through the vocal cords. However, most of the published randomized controlled trials did not use any premedication before LISA.[5,20,21] Also, in studies investigating LISA practices in different countries, apart from the Nordic countries, LISA is often performed in awake patients.[22-24] Only in the last 3 years, reports started to appear in the literature using different kinds of premedication prior to LISA.[25-28] The performance of LISA in awake patients might be considered a relapse in neonatal medicine.[20]

We performed this observational cohort study to assess the success rate and quality of the technical conditions, and the vital parameter response in preterm newborns undergoing a LISA procedure without sedative premedication.

METHODS

Study design and patients

We conducted a prospective monocentric observational study on the level III neonatal intensive care unit (NICU) at Máxima Medical Center Veldhoven, the Netherlands, between January 2016 and February 2018. Patients <32 weeks' gestation were included in the study if they had RDS and were treated with LISA. We only included every first LISA procedure per patient. LISA for treatment of RDS was implemented into daily practice in our department in 2014 and is since then standard of care. LISA is performed in infants with a gestational age (GA) less than 32 weeks with clinical signs of RDS, respiratory support with nasal CPAP with a positive end-expiratory pressure of at least 6 cm H_2O, and an oxygen requirement of 30% or more to maintain SpO_2 levels between 88 and 95%.

Description of the LISA procedure

LISA procedures were performed according to a local standardized protocol. Prior to LISA, patients received a loading dose of caffeine to support the respiratory drive. A dose of atropine 10 µg/kg was administered 5 to 10 min before start of the procedure to prevent reflex bradycardia during laryngoscopy and catheter placement. About 1 to 2 minutes before start of the procedure, sucrose 20% (0.1 ml/kg) was administered in the cheek pouch and facilitated tucking was applied. During the procedure, swaddling was performed to contain the infant and promote comfort. Sedative premedication was not used. A laryngoscope was then used for visualization of the vocal cords and placement of the catheter. At the start of the study we used a 5F umbilical catheter which was placed between the vocal cords with the use of a Magyll forceps. During the study we started to use a shorter and stiffer LISA catheter (Chiesi Pharmaceuticals, Parma, Italy), for which the use of a Magyll forceps was no longer needed. After placement of either catheter, surfactant (Curosurf, 150–200 mg/kg) was instilled over a period of 1–3 min while the patient was spontaneously breathing on nasal CPAP. During surfactant instillation, aspiration was done via the nasogastric tube to check for surfactant spill. After surfactant instillation was complete, the catheter was immediately removed.

Data collection

We collected the following patient characteristics: gestational age, birth weight, postnatal age at the LISA procedure and gender. Data regarding starting time of the LISA procedure, the quality of technical conditions using a standardized scale, the number of attempts, reasons for failed attempts, and function of the operator of the procedure were collected during and immediately after the procedure on a standardized registration form.

In accordance with the NEAR4KIDS registry definitions of intubation encounters and attempts,[29] we defined a LISA procedure as one complete procedure of airway management intervention including the administration of surfactant. An attempt was defined as one episode of laryngoscopy, beginning with the insertion of the laryngoscope into the patient's mouth and ending when the laryngoscope was removed. A successful attempt was defined as an episode of laryngoscopy in which the complete amount of surfactant could be administered. An attempt failed if not the complete dose of surfactant could be administered and another laryngoscopy episode was needed to complete surfactant administration. Quality of technical conditions was assessed by the operator of the procedure with the Viby-Mogensen intubation score.[30] One missing item was allowed, if more than one item of the intubation score was missing, quality of technical conditions could not be judged. Good technical quality was defined as a score on each item ≤2. A score on one or more items ≥3 implied inadequate technical quality.

Vital parameters

In all infants admitted to the NICU vital parameters are continuously monitored using Intellivue MXI 800 patient monitors (Philips, Hamburg, Germany). All data are saved to a data warehouse system with a sampling rate of 1 Hz. For the purpose of this study, data were extracted from 20 min before until 30 min after start of the LISA procedure. Data were averaged per minute. Baseline heart rate and oxygen saturation were calculated as median heart rate and oxygen saturation in the period from 20 min to 10 min before start of the LISA procedure. The period from 10 min before to start of the LISA procedure was discarded as in this period atropine was administered and nursing handling was needed to install the patient properly for the LISA procedure. Changes in heart rate and oxygen saturation in the 30 min after the start of LISA in relation to baseline were calculated. Besides this, changes in heart rate and oxygen saturation after the start of LISA compared with baseline were calculated for patients with good versus patients with inadequate technical quality, and for patients with success versus patients with failure of the first attempt.

Statistical analysis

SPSS (IBM SPSS Statistics for Windows, version 22.0, Armonk, NY, USA) was used to analyze the data. Relevant patient data were reported as numbers with percentages for qualitative variables and median and interquartile ranges for quantitative variables. Comparison between groups was performed with the Mann–Whitney U test for continuous variables and the Pearson Chi square test or Fisher's exact test, as appropriate, for categorical variables. Comparison of vital parameters between baseline and different time points after baseline within the same group of patients was performed with a paired t-test.

Ethical approval

For this observational study we received a waiver for formal ethical approval (Medical Ethical Committee, Máxima Medical Center, Veldhoven, the Netherlands, No. N18.095) according to the Dutch Law of Research with Humans. No additional parental consent was required.

RESULTS

Study population

Inclusion of patients is shown in the study flow chart in Figure 1. During the study period LISA was performed in 111 patients with a GA <32 weeks. Twenty-five patients were excluded because the standardized registration form was not completed and therefore data regarding quality of technical conditions and success of LISA attempts were lacking, leaving 86 patients to be included. In 29 patients, data on vital parameters were not available in data warehouse and in 20 patients these data could not be retrieved because the precise starting time of LISA was lacking. Therefore, heart rate and oxygen saturation data from 20 min before until 30 min after start of LISA were available in 37 patients. Patient characteristics of the study population are shown in Table 1. Patients in whom vital parameter data were lacking, had younger gestational and postnatal ages compared to patients with available data.

Table 1. Patient characteristics

	Total study population	Vital parameter analysis	No vital parameter analysis	p-value
	n = 86	n = 37	n = 49	
Gestational age (week), median (IQR)	28.3 (26.6-29.7)	29.0 (27.1-30.0)	27.9 (25.7-29.1)	0.007
Birth weight (g), median (IQR)	1,015 (769-1,305)	1,120 (853-1,320)	995 (715-1,255)	0.12
Birth weight <10th percentile, n (%)	25 (29)	13 (35)	12 (25)	0.34
Postnatal age (hr), median (IQR)	3.3 (2.1-8.5)	5.4 (2.5-13.2)	2.7 (1.9-5.9)[a]	0.01
Male gender, n (%)	49 (57)	23 (62)	26 (53)	0.51

[a]Missing data in 7 patients.

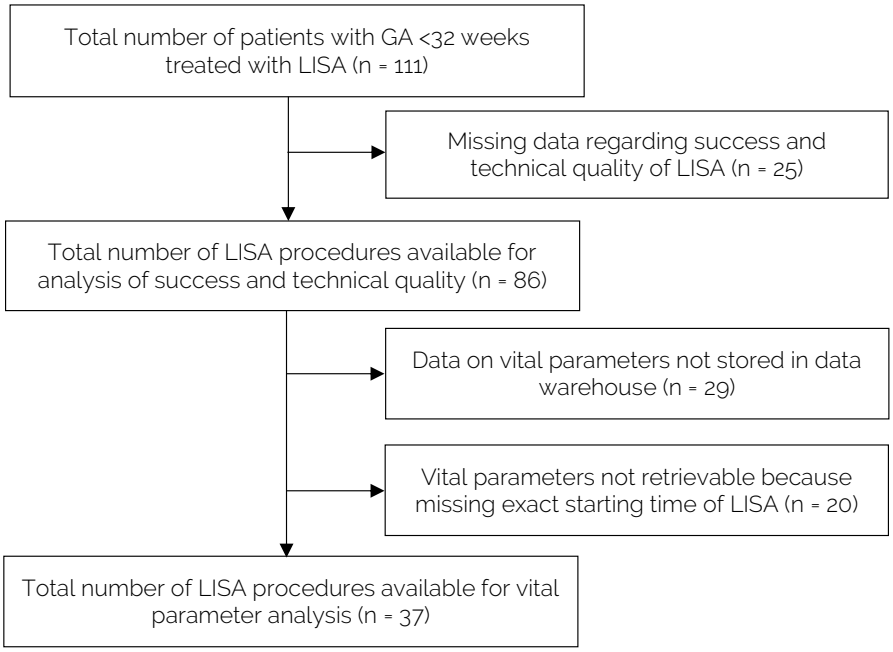

Figure 1. Study flow chart

Success of LISA attempts

The LISA procedure was successful at the first attempt in only 45 patients (52%). In 32 patients (37%) 2 attempts were required and in 9 patients (11%) 3 attempts were needed. Reported reasons for failure of first attempts were: inability to visualize the vocal cords in 11 (27%), interruption of the procedure because of significant surfactant spill in 4 (10%), dislocation of the catheter during surfactant administration in 4 (10%), inability to introduce the catheter between the vocal cords in 5 (12%), worsening condition of the patient in 5 (12%), patient resistance in 1 (2%), and other reasons in 4 attempts (10%). In 7 attempts (17%) the reason for failure was not reported. The first attempt was performed by a pediatric resident in 7 procedures (8%), a neonatal nurse specialist in 22 procedures (26%), a fellow in neonatology in 10 procedures (12%) and a neonatologist in 46 procedures (53%). Pediatric residents were successful in only 2 attempts (29%), neonatal nurse specialists were successful in 7 attempts (32%), fellows in neonatology were successful in 3 attempts (30%) and neonatologists were successful in 33 attempts (72%) ($p = 0.003$).

Table 2a shows patient characteristics and experience of the performer in successful and failed first attempts. These results show there are no statistically significant differences in patient characteristics between LISA procedures in which the first attempt was successful

compared to LISA procedures in which the first attempt failed. However, in procedures in which the first attempt was successful, the performer of the procedure was significantly more often a neonatologist than in procedures in which the first attempt failed (73% versus 33%, p <0.001).

Table 2a. Patient characteristics and performer experience in relation to success rate

	Success n = 45	Failure n = 41	p-value
Patient characteristics			
Gestational age (week), median (IQR)	28.3 (26.7-29.4)	28.4 (25.9-29.9)	0.92
Birth weight (g), median (IQR)	1,030 (763-1,300)	1,000 (750-1,328)	0.94
Birth weight < 10th percentile, n (%)	13 (29)	12 (29)	1.00
Postnatal age (h), median (IQR)	3.3 (2.1-11.6)	3.3 (2.1-7.3)	0.58
Male gender, n (%)	25 (56)	24 (59)	0.83
Procedure characteristics			
First attempt by neonatologist, n (%)	33 (73)	13 (33)[a]	<0.001
Good technical quality, n (%)	34 (76)	11 (35)[b]	0.001

[a]For one procedure the performer was not reported; [b]For ten procedures quality of technical conditions was missing.

Technical quality assessment

Information about the quality of technical conditions was available for 76 LISA procedures (88%). Quality was good in 45 procedures (59%) and inadequate in 31 procedures (41%). Table 2b shows the patient characteristics and experience of the performer in procedures with good and with inadequate quality assessment. There were no statistically significant differences in patient characteristics or in the level of experience of the performer between procedures with good and with inadequate technical quality. Quality assessment was, however, related to the success of the first attempt. Of the 45 procedures in which the first attempt was successful, technical quality was good in 34 procedures (76%), whereas of the 31 procedures in which the first attempt failed, only 11 procedures (35%) had good technical quality (p = 0.001).

Vital parameters

Figure 2 shows heart rate and oxygen saturation at baseline and at different time points after start of the LISA procedure. Heart rate significantly increased compared to baseline at all time points with the exception of t = 1 min. Oxygen saturation did not change significantly from baseline at all time points with the exception of t = 1 and t = 2 min, in which oxygen saturation was significantly lower compared to baseline.

Table 2b. Patient characteristics and performer experience in relation to quality assessment

	Good quality n = 45	Inadequate quality n = 31	p-value
Patient characteristics			
Gestational age (week), median (IQR)	28.3 (26.6-29.6)	28.1 (27.0-30.0)	0.70
Birth weight (g), median (IQR)	1,050 (788-1,313)	1,000 (800-1,300)	0.76
Birth weight < 10th percentile, n (%)	12 (27)	12 (39)	0.32
Postnatal age (h), median (IQR)	3.5 (2.5-9.6)	3.2 (2.0-10.7)	0.53
Male gender, n (%)	24 (53)	21 (68)	0.24
Procedure characteristics			
First attempt by neonatologist, n (%)	29 (64)	16 (52)	0.34
Success of first attempt, n (%)	34 (76)	11 (35)	0.001

In only two patients (5%) there was a brief period of bradycardia <100/min in the first 10 min after start of the LISA procedure. In both patients, heart rate restored within 1 min and never dropped below 80/min. Desaturations were more frequent: in 20 patients (54%) oxygen saturation dropped below 80% on one or more occasions in the first 10 min after start of LISA.

Figure 3 shows heart rate and oxygen saturation in relation to the success rate of the first attempt and technical quality of each LISA procedure. Heart rate and oxygen saturation did not differ significantly between patients with success versus failure of the first attempt and between good versus inadequate technical quality. There was, however, a significant difference in the time until the deepest drop in oxygen saturation between patients with good versus inadequate technical quality. In patients with good technical quality the lowest oxygen saturation occurred after a median of 2 min after start of LISA versus a median of 5.5 min for patients in whom the technical quality was inadequate (p = 0.018). In patients in whom the first attempt was successful, the deepest drop in oxygen saturation occurred at a median of 4 min, and in patients in whom the first attempt failed the deepest drop in oxygen saturation occurred at median of 2 min. This difference, however, is not statistically significant (p = 0.136).

Oxygen desaturations below 80% occurred in 13/19 patients (68%) with good quality conditions and in 7/15 patients (47%) with inacceptable quality (p = 0.30). In procedures with a successful first attempt (n = 19), desaturations below 80% occurred in 13 patients (68%), while in procedures in which the first attempt failed (n = 18) these desaturations occurred in 7 patients (39%). This difference was also not statistically significant (p = 0.10).

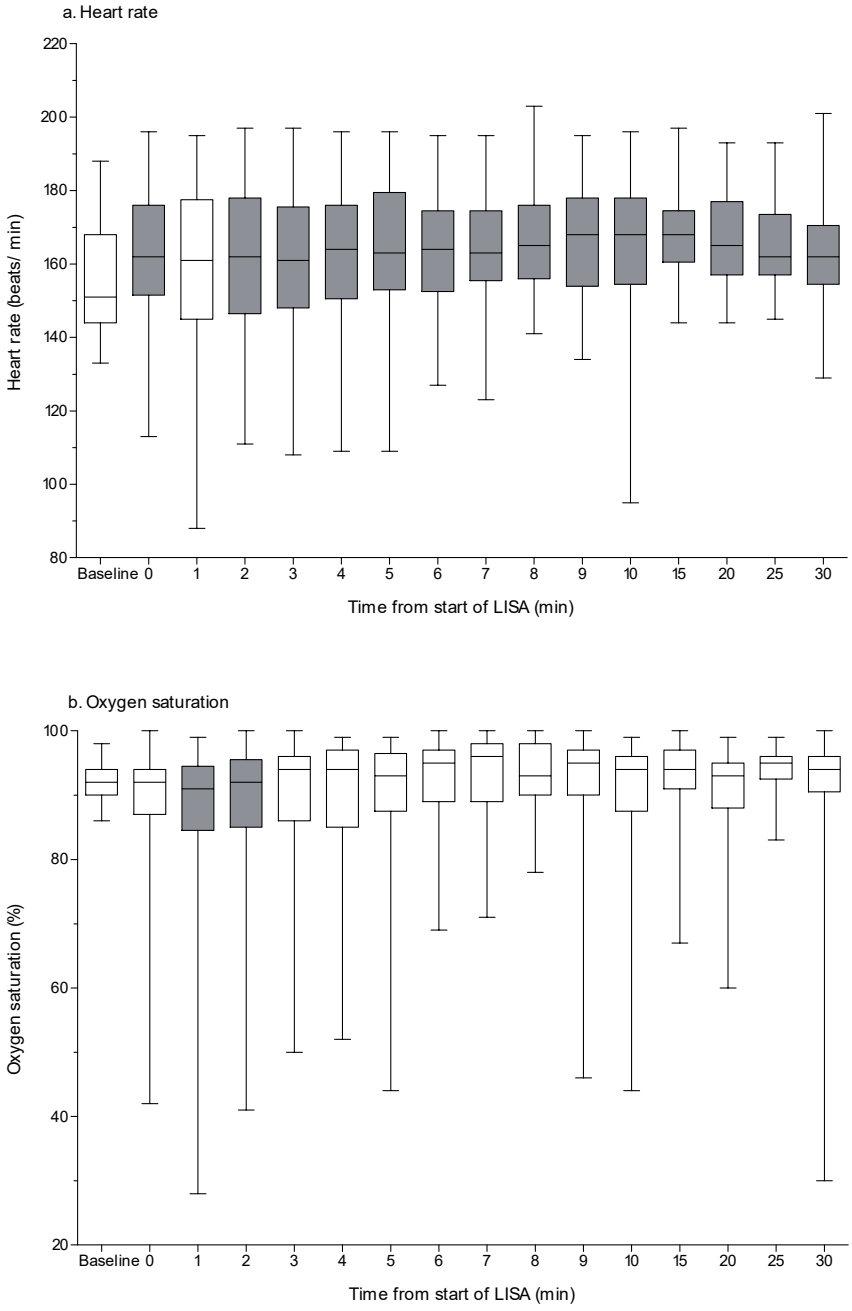

Figure 2. Heart rate and oxygen saturation at baseline and after start LISA
Dark grey bars indicate significant differences ($p < 0.05$) compared to baseline.

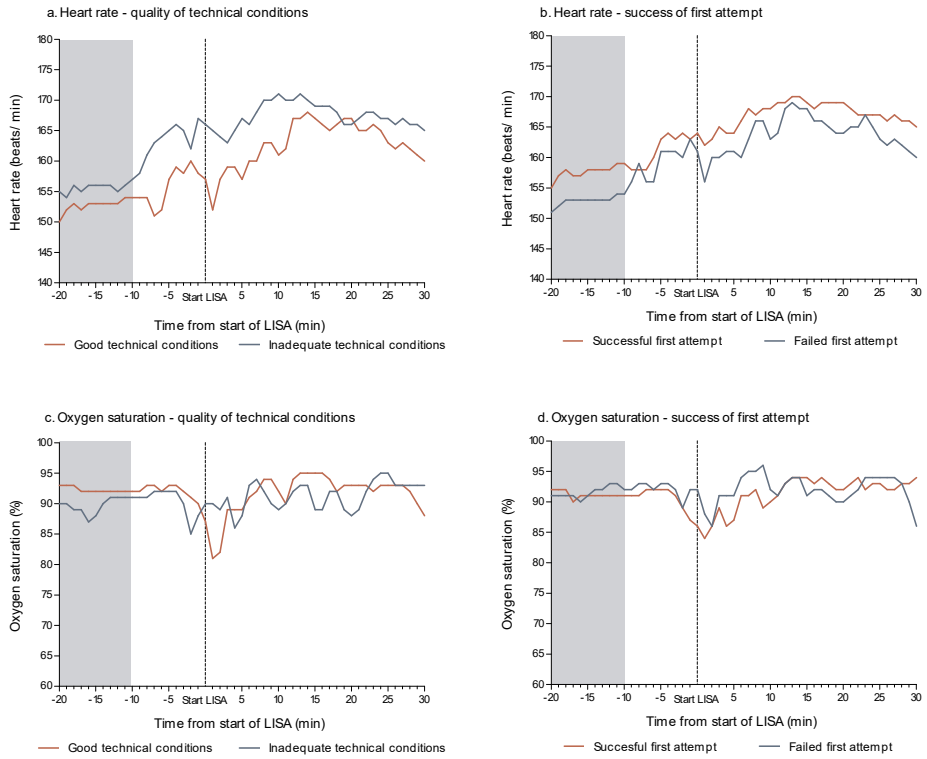

Figure 3. Heart rate and oxygen saturation in relation to the success rate and quality of intubation
Light grey areas indicate the period from which baseline heart rate and oxygen saturation were calculated.

DISCUSSION

This observational study was performed to assess the quality and effect on vital parameters of LISA procedures performed without the use of sedative premedication. LISA performed in awake patients had a low success rate of the first attempt, and the technical quality was frequently inadequate. Also, there was a significant correlation between failure of the first attempt and the quality of technical conditions, suggesting patient discomfort and intolerance as a cause for first attempt failure. Besides this, there was a high frequency of oxygen desaturations. Combined with the extensive existing evidence on the harmful effects of awake laryngoscopy during endotracheal intubation, our results emphasize the need for better pain reduction and patient comfort during LISA by using sedative premedication.

From 2016 onwards several reports have appeared in the literature using premedication during LISA. Although different strategies of sedative premedication were used, these reports unanimously showed better patient comfort in patients treated with premedication.[25-27] However, sedative premedication also has adverse effects. In one retrospective study and one randomized controlled trial, propofol as premedication for LISA has shown to increase the need for non-invasive intermittent positive pressure ventilation.[25,26] Although the need for endotracheal intubation was not increased in patients treated with propofol, the frequency of mechanical ventilation in the first 72 hours of life was higher compared to those that did not receive premedication.[20] Ketamine as premedication led to a relatively high need for endotracheal intubation.[27] Since LISA failure causes a higher median number of days on mechanical ventilation, a higher incidence of supplemental oxygen at day 28 and a 20% lower survival without serious adverse events,[31] it is important to use sedative premedication that has little to no effect on the respiratory drive in order to prevent LISA failure.

Awake laryngoscopy has considerable effects on vital parameters such as oxygen saturation and heart rate. In our study population, oxygen desaturations <80% in the first 10 min from start of LISA occurred in 54% of patients. This percentage is lower compared to the studies using premedication prior to LISA.[25-28] The high incidence of oxygen desaturations in premedicated patients is most probably not due to laryngoscopy, but caused by a pronounced suppression in respiratory drive by the sedative premedication. Besides this, during LISA oxygen desaturations are not only an effect of laryngoscopy but are also caused by the administration of surfactant. The increase in heart rate found in our study is at least partly due to the administration of atropine prior to LISA and is therefore not a clear indicator of patient stress and discomfort. The administration of atropine did, however, prevent patients from developing bradycardia compared to the study of Dekker et al. who did not use atropine.[26]

In endotracheal intubation, and presumably also in LISA, the use of premedication can decrease the number of attempts needed for success,[12,13,17] and improve the quality of technical condtions.[32,33] In half of all our LISA procedures more than one laryngoscopy episode was needed for completion of the procedure. This success rate was comparable to success rates in studies using premedication prior to LISA,[26,27] as well as studies using propofol as premedication before endotracheal intubation.[34,35] Inadequate quality assessment was found in 41% of procedures. Technical quality seems considerably better when ketamine is used prior to LISA.[27] To our opinion, the absence of improved success rate after premedication does not mean premedication should not be used. It indicates that we have to do better in premedicated LISA procedures and endotracheal intubation as well.

In summary, comparison of our findings in awake LISA with studies using sedative premedication prior to LISA shows that success rates and effects on vital parameters are comparable. This should not encourage neonatologists to keep on performing LISA in awake patients. There is enough evidence on the harmful effects of awake laryngoscopy during endotracheal intubation and there is no reason to believe these effects would be different in the context of a LISA procedure. LISA, therefore, should always be performed with the use of sedative premedication. This premedication, however, should have the least effect on the respiratory drive and should not hamper LISA success. More research is obviously needed to determine the best premedication strategy.

Success of intubation attempts is not only determined by the use of sedative premedication. Level of experience of the operator is also an important determinator of success.[36] In our study, we found a significant correlation between the success of LISA and the level of experience of the operator. Of all LISA procedures in which the first attempt was successful, it was performed by a neonatologist in 73%, compared with 33% of the procedures in which the first attempt failed. For endotracheal intubation it is known that the use of premedication improves the success rates of inexperienced operators.[37,38] It is likely that this is also applicable for LISA. Irrespective of the use of premedication, operator level of experience and number of attempts needed are important factors increasing the odds for endotracheal intubation related adverse events.[36,39,40] Although there are no studies evaluating the occurrence of LISA related adverse events, it is presumable that the incidence of adverse events during LISA is also influenced by these factors. The operator for LISA should, therefore, be carefully chosen.

Lack of data on success and technical quality because of missing registration forms led to the exclusion of almost 25% of patients that underwent LISA in our study, which could have led to selection bias. The excluded population, however, had comparable baseline characteristics compared with the included patients. The included patients are a good reflection of the total population of preterm infants undergoing LISA and, therefore, our results have good generalizability.

Our study has several limitations. First limitation is the use of atropine prior to LISA. One of the goals of our study was to determine the effects of awake LISA on vital parameters. We found a significant increase in heart rate at all time points after start of LISA, but this is most probably due to the administration of atropine, rather than a reflection of patient stress and discomfort. Nevertheless, we encourage the use of atropine prior to LISA, since it prevents the occurrence of bradycardia and its related risk for hypoxia.

Second limitation is the lack of vital parameter data in 59% of included patients. Patients with available data had significantly higher gestational and postnatal ages compared to patients in whom vital parameter data were not available. Since we found no influence of gestational and postnatal age on the success rate and technical quality, we would not expect the effects of awake LISA on vital parameters to be different in younger compared to older infants. The availability of vital parameter data in only a small proportion of patients, therefore, will most likely not have affected the validity of our findings. Other limitations are the lack of blood pressure data, which could have helped make a distinction between atropine effect and stress in patients with a significant elevation of heart rate, and the lack of objective measurements of pain and discomfort.

CONCLUSION

In our study of LISA procedures performed without sedative premedication, the success rate of the first attempt was only 52%, the technical quality was frequently inadequate, and there was a high incidence of oxygen desaturations. Although providing patient comfort should be a key factor in neonatology, the adverse effects of performing LISA without premedication should be carefully weighed against the negative effects and risks of administering sedative premedication before LISA. Other forms of premedication with lesser effect on the respiratory drive need to be investigated. The use of atropine during LISA resulted in a very low incidence of bradycardia and should therefore be strongly considered, regardless of the use of sedative premedication.

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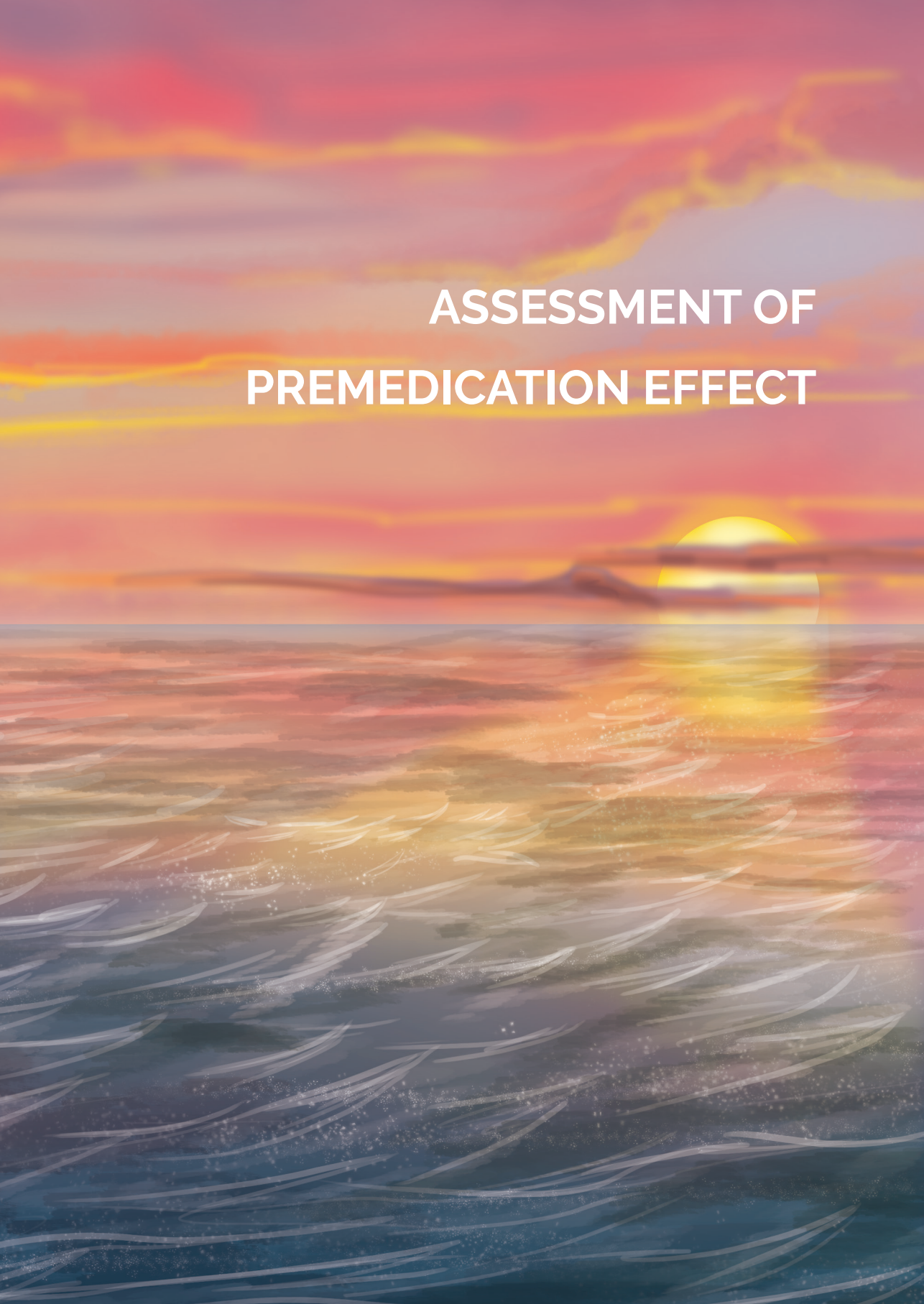
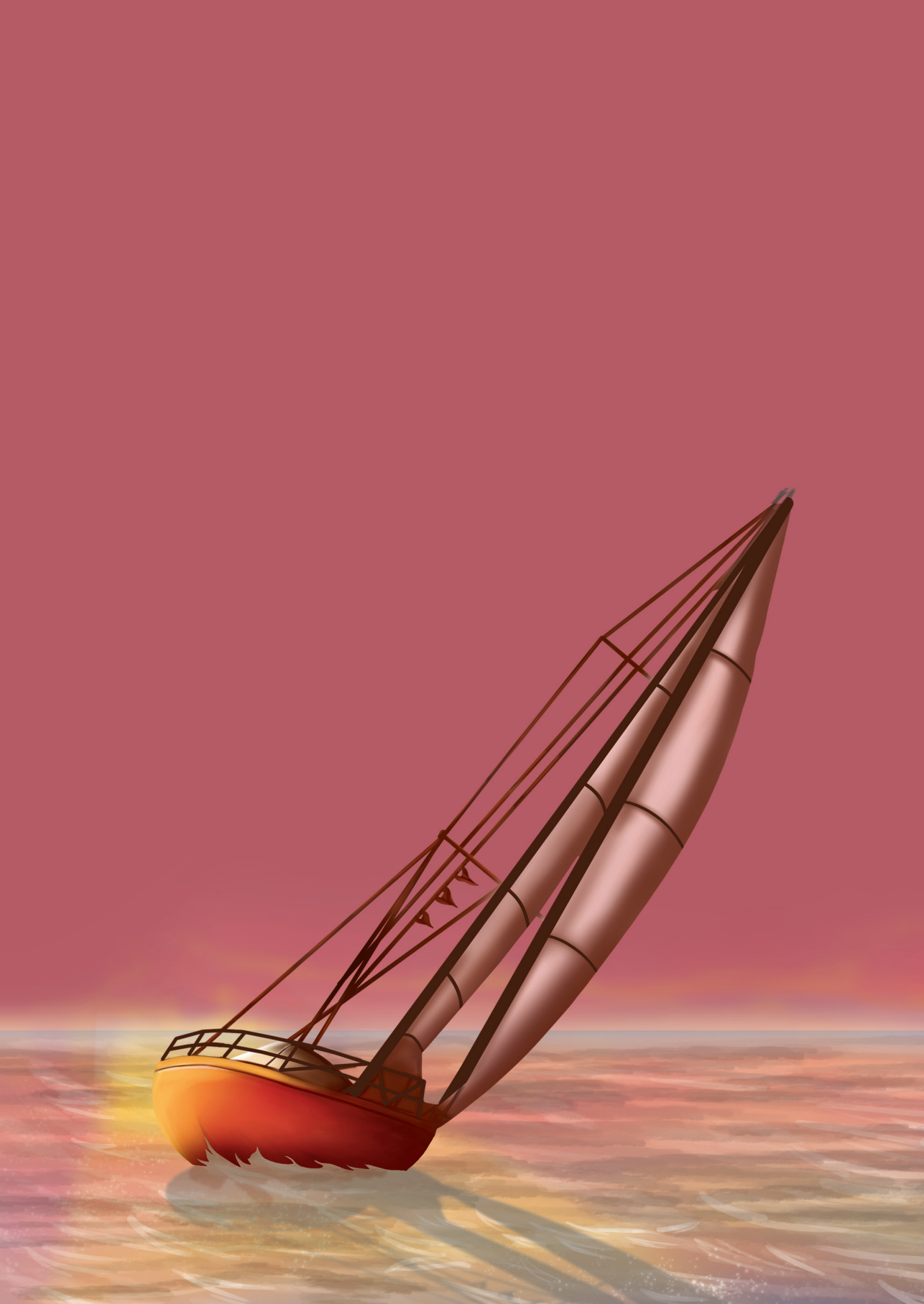


ASSESSMENT OF PREMEDICATION EFFECT



CHAPTER 5

ASSESSMENT OF SEDATION LEVEL PRIOR TO NEONATAL INTUBATION: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Adequate premedication before neonatal endotracheal intubation reduces pain, stress, and adverse physiological responses, diminishes duration and number of attempts at intubation, and prevents traumatic airway injury. Therefore, intubation should not be started until an adequate level of sedation is reached. It is not clear how this should be measured in the clinical situation.

Objectives: The aim of this study is to provide a systematic review on the usability and validity of scoring systems or other objective parameters to evaluate the level of sedation before intubation in neonates. Secondary aims were to describe parameters that are used to determine the level of sedation and criteria on which the decision to proceed with intubation is based.

Methods: Literature was searched (January 2017) in the following electronic databases: Embase, Medline, Web of Sciences, Cochrane Central Registrar of Controlled Trials, Pubmed Publisher, and Google Scolar.

Results: From 1653 hits, 20 studies were finally included in the systematic review. In 7 studies, intubation was started after a predefined time period; in 1 study preoxygenation was the criterion to start with intubation; and in 12 studies, intubation was started in case of adequate sedation and/or relaxation. Only 4 studies described the use of 3 different objective scoring systems, all in the neonatal intensive care unit, which are not validated.

Conclusion: No validated scoring systems to assess the level of sedation prior to intubation in newborns are available in the literature. Three objective sedation assessment tools seem promising but need further validation before they can be implemented in research and clinical settings.

INTRODUCTION

A significant proportion of preterm and critically ill newborn infants needs endotracheal intubation at some point during their admission to the Neonatal Intensive Care Unit (NICU) or because of anesthesia. Indications range from respiratory insufficiency in case of pulmonary morbidity, sepsis, or necrotizing enterocolitis, and the administration of surfactant, to surgical procedures such as bowel surgery, surgical closure of a patent ductus arteriosus, laser coagulopathy in case of retinopathy of prematurity, or placement of a surgical central venous catheter. Endotracheal intubation is a painful and stressful procedure and often is associated with adverse physiological responses such as bradycardia, hypoxemia, systemic hypertension, and intracranial hypertension.[1-7] The use of premedication before intubation reduces the risk of these adverse events, and also reduces the duration and number of attempts needed for successful intubation and prevents traumatic injury to face, eyes, gums, tongue, and glottic structures.[6-11] Neonatal intubation should therefore be preceded by sedative premedication.

The goal of administering premedication is to achieve a proper level of sedation before intubation is started or muscle relaxants are administered. Still the question is how this level of sedation should be defined and how this should be measured in the clinical situation.

OBJECTIVES

Our primary objective was to provide a systematic review of studies assessing the usability and validity of objective scoring systems or parameters to evaluate the level of sedation before intubation in newborn infants. Because we presumed that very few studies have addressed this issue, our secondary objective was to describe common practice, addressing the following two questions:

1. On what parameter(s) and/or criteria is the decision to proceed with intubation after the administration of premedication based?
2. Which (objective) scores or other parameters are used to determine the level of sedation after administration of premedication?

MATERIALS AND METHODS

Study design

This systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[12]

Criteria for considering studies for this review

Types of studies

For our primary objective, eligible for inclusion were randomized controlled trials (RCTs), quasi-RTCs, controlled clinical trials, and observational studies evaluating the use of objective scoring systems or parameters to assess level of sedation. For our secondary objectives, also single-case studies, poster presentations, editorials, and reviews were eligible for inclusion, provided these extensively reported on the complete procedure from administration of premedication to start of the intubation. Availability of full text was imperative.

Types of study population

The target population consisted of preterm and term neonates who needed endotracheal intubation.

Types of interventions

For the primary objective, studies evaluating an objective score or parameter to assess the level of sedation after administration of premedication were included. For the secondary objectives, studies addressing any type of intervention were included.

Data collection and analysis

Electronic searches

The following electronic databases were searched: Embase, Medline, Web of Science, Cochrane Central Registrar of Controlled Trials, Pubmed Publisher, and Google Scholar. The search strategies are outlined in Table 1. There were no restrictions on the basis of publication date or publication status. The search strategy also had no restriction in language. The search was performed on January 27, 2017.

Selection of studies

Two authors (EdK and NH) independently assessed titles and abstracts of the search results. Full copies of all potentially relevant studies were obtained. Both authors made a decision on final inclusion after retrieval of full copies independently. Disagreements were resolved by consensus; if necessary, a third author was consulted (SS). Only articles written in English, Dutch, German, and French were selected.

Table 1. Search strategies

Electronic database	Search strategy
Embase	(intubation/de OR 'respiratory tract intubation'/exp OR (intubat*):ab,ti) AND (newborn/de OR 'newborn intensive care'/exp OR prematurity/de OR 'low birth weight'/exp OR 'newborn care'/de OR (newborn* OR (new* NEXT/1 born*) OR neonat* OR nicu OR nicus OR prematur* OR preterm* OR 'low birth weight' OR lbw OR vlbw OR elbw):ab,ti) AND (premedication/exp OR 'hypnotic sedative agent'/exp OR 'sedative agent'/exp OR 'conscious sedation'/de OR 'deep sedation'/de OR 'anesthetic agent'/exp OR 'muscle relaxation'/de OR 'muscle relaxant agent'/exp OR 'neuromuscular blocking agent'/exp OR (premedicat* OR sedat* OR anesthetic* OR anaesthetic* OR ((musc* OR neuromusc*) NEAR/3 (relax* OR block*))):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ('cesarean section'/de OR pregnancy/exp OR 'pregnant woman'/de OR (cesarean* OR caesarean* OR pregnan*):ab,ti)
Medline	(intubation/ OR "Intubation, Intratracheal"/ OR (intubat*).ab,ti.) AND (exp infant, newborn/ OR "Intensive Care Units, Neonatal"/ OR "Intensive Care, Neonatal"/ OR (newborn* OR (new* ADJ born*) OR neonat* OR nicu OR nicus OR prematur* OR preterm* OR "low birth weight" OR lbw OR vlbw OR elbw).ab,ti.) AND (premedication/ OR exp "Hypnotics and Sedatives"/ OR "conscious sedation"/ OR "deep sedation"/ OR exp "anesthetics"/ OR "muscle relaxation"/ OR exp "Neuromuscular Agents"/ OR (premedicat* OR sedat* OR anesthetic* OR anaesthetic* OR ((musc* OR neuromusc*) ADJ3 (relax* OR block*))).ab,ti.) NOT (exp animals/ NOT humans/) NOT ("cesarean section"/ OR exp pregnancy/ OR "pregnant women"/ OR (cesarean* OR caesarean* OR pregnan*).ab,ti.)
Cochrane	((intubat*):ab,ti) AND ((newborn* OR (new* NEXT/1 born*) OR neonat* OR nicu OR nicus OR prematur* OR preterm* OR 'low birth weight' OR lbw OR vlbw OR elbw):ab,ti) AND ((premedicat* OR sedat* OR anesthetic* OR anaesthetic* OR ((musc* OR neuromusc*) NEAR/3 (relax* OR block*))):ab,ti) NOT ((cesarean* OR caesarean* OR pregnan*):ab,ti)
Web of Science	TS=((((intubat*)) AND ((newborn* OR (new* NEAR/1 born*) OR neonat* OR nicu OR nicus OR prematur* OR preterm* OR "low birth weight" OR lbw OR vlbw OR elbw)) AND ((premedicat* OR sedat* OR anesthetic* OR anaesthetic* OR ((musc* OR neuromusc*) NEAR/2 (relax* OR block*)))) NOT ((cesarean* OR caesarean* OR pregnan*)) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine) NOT (human* OR child* OR patient*)))
Google Scolar	Intubation|intubated newborn|newborns|neonates|neonatal|nicu|nicus|premature|preterm|"low birth weight"|lbw|vlbw|elbw premedication|sedation|anesthetic|anaesthetic|"muscular|neuromuscular relaxation|blockers" -cesarean -caesarean -pregnancy -pregnant

Data extraction

Two authors (EdK and NH) extracted details of the included studies independently. The following data were extracted: use of premedication, used drugs or combination of drugs, scores or parameters determining the decision to proceed with intubation, sedation as parameter to proceed with intubation, actions undertaken in case of insufficient sedation.

Quality appraisal of individual studies

Because no studies were found reporting on the usability and validity of scoring systems or other parameters to assess the level of sedation, and we thus only report on common practice as described in the methods sections of the reports, evaluation of the methodological quality and the risk of bias was not relevant.

RESULTS

Study selection

A flowchart of study selection is provided in Figure 1. The initial electronic database search yielded 2597 records, which number was reduced to 1652 after duplicates were removed. One additional record found in reference lists was added. Thus, the titles and abstract of in total 1653 records were screened on relevance to the primary and secondary objectives. None of the studies appeared relevant to the primary objective. Regarding the secondary objective, full text was obtained from 75 records and 1578 records were excluded. Of these 75 records, 5 were excluded because of language restriction (1 record) or unavailability (4 records). Of the remaining 70 records, full text was read. The studies' methods sections were screened for information about parameters on which the decision to start with intubation was based. Twenty studies provided this information and these were included in the final analysis of our secondary objective.

Study characteristics and results of individual studies

Table 2 shows the characteristics of the 20 included studies. In 12 studies, the decision to proceed with intubation after the administration of premedication was based on the degree of sedation or relaxation.[7,13-23] Nevertheless, no more than 4 of these 12 studies used an objective scoring system.[13-16] In one other of the 12 studies, disappearance of the eyelash reflex was considered an indicator of hypnosis and therefore as the criterion to start with intubation.[21] In the control group, loss of muscle tone was the criterion to start with intubation.[21] The methods section did not describe, however, how muscle relaxation was rated. In the remaining 7 studies that based the start of the intubation on the degree of sedation and/or relaxation, it was not clear if sedation and/or relaxation were rated either in an objective or a rather subjective way.[7,17-20,22,23] In 8 of the 12 studies,

the intubating clinician's observation of insufficient sedation led to the administration of more premedication to achieve an adequate level of sedation and/or relaxation.[7,13,14,17-19,21,22] In the remaining four studies, this was not mentioned at all.[15,16,20,23]

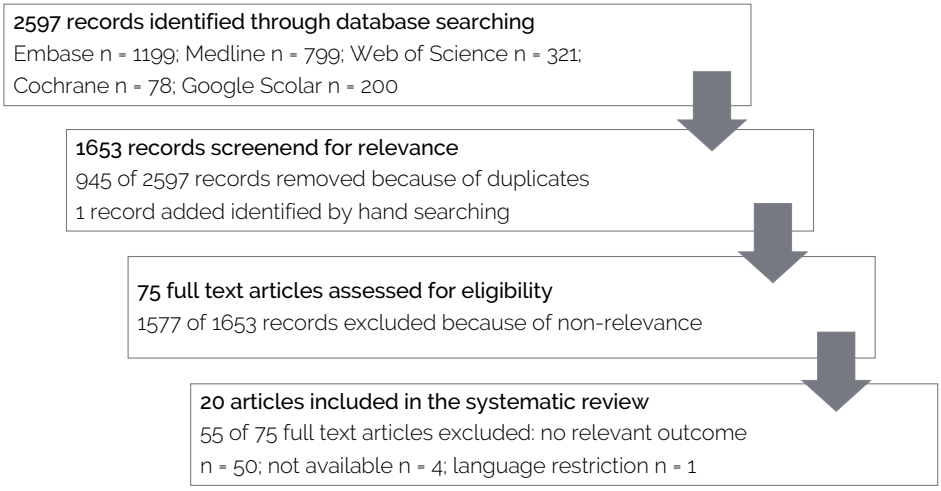

Figure 1. Flowchart of included and excluded studies

In 7 of all 20 included studies, intubation was started after a certain period of time had elapsed after the administration of premedication.[5,6,24-28] The methods section of these studies neither made clear if level of sedation also played a role, nor if all patients were adequately sedated upon start of the intubation procedure. In one study, preoxygenation was the leading parameter to start with intubation.[29]

Only 4 of the 20 studies used an objective scoring system to assess the level of sedation before proceeding with intubation. These objective scoring systems are outlined in Table 3. The first scoring system is a sedation score used in two different reports. Smits et al. used this score in their dose-finding study for propofol in newborns and De Kort et al. used the score in a study on the use of remifentanil in preterm infants undergoing the INSURE procedure.[13,14] The score is adopted from the study of Naulaers et al. into the effectiveness of methohexital as premedication for elective intubation.[15] The level of sedation is assessed by the motor response to a firm stimulus by rubbing of the feet (1 = spontaneous movement, 2 = moves on slight touch, 3 = moves on stimulus, 4 = no movement). In both studies, sedation was presumed to be effective with scores 3 and 4, upon which intubation was started.

Table 2. Characteristics of included studies

First author, year, country	Study design	Premedication
Smits A, 2016, Belgium	Prospective observational	Propofol
De Kort E, 2016, the Netherlands	Prospective observational	Remifentanil
Avino D, 2014, Belgium	Non-inferiority randomized trial	SG: remifentanil CG: morphine, atropine, midazolam
Baleine J, 2014, France	Prospective observational	Nasal midazolam
Durrmeyer X, 2014, France	Prospective observational	Atropine, sufentanil and atracurium
Thall PF, 2014, USA	Not applicable	Not applicable
Simons S, 2013, the Netherlands	Prospective observational	Propofol
Penido MG, 2011, Brazil	Double blinded randomized trial	SG: propofol, remifentanil CG: propofol, midazolam
Choong K, 2010, Canada	Double-blinded randomized controlled trial	SG: remifentanil, atropine, placebo CG: fentanyl, atropine, succinylcholine
Welzing L, 2010 Germany	Prospective observational	Propofol
Lemyre B, 2009, Canada	Prospective observational	Atropine, fentanyl, succinylcholine (only in GA ≥34 weeks)
Van Looy, 2008, USA	Prospective observational	Midazolam and fentanyl
Ghanta S, 2007, Australia	Randomized, open-label, controlled trial	SG: propofol CG: morphine, atropine, suxamethonium
Dempsey E, 2006, Ireland	Prospective observational	Mivacurium and fentanyl
Milesi C, 2006, France	Prospective observational	Nitrous oxide
Roberts K, 2006, USA	Randomized controlled trial	SG: atropine, fentanyl, mivacurium CG: atropine, fentanyl

Parameter for start intubation	Start intubation	Consequences insufficient sedation/relaxation
Sedation and relaxation	Good sedation and relaxation scores	Additional propofol in case of unsatisfactory relaxation and sedation according to physician
Sedation	Good sedation scores	Additional remifentanil until good sedation score
Time	SG: after complete remifentanil infusion; CG: 3 min after midazolam infusion	
Sedation	At hypnosis, muscle relaxation or apnea	Second dose in case of arousal at introduction of tube or excessively awake at 5 min
Relaxation	At onset of paralysis	Extra atracurium (up to predefined maximum)
Sedation	Good sedation score	Not applicable
Sedation	When sedation was scored yes by treating physician	Extra propofol (up to a maximum of 3 doses)
Time	2 min after remifentanil infusion	
Time	30 s after last drug administration	
Time	75 s after propofol administration	
Relaxation	Cessation of spontaneous movements (succinylcholine group) or sufficient relaxation	None mentioned
Time	1-2 min after medication administration	Another dose of fentanyl in case of 3 failed attempts
Hypnosis and relaxation	SG: disappearance of eyelash reflex CG: muscle relaxation	SG: 1 extra dose of propofol CG: repeating doses of suxamethonium
Preoxygenation	Saturation > 95%, typically 2 min after fentanyl infusion	
Relaxation	At suppression of muscle tone (cessation of movements and hypotonia limbs and jaw)	
SG: relaxation CG: time	SG: once spontaneous movements had ceased CG: after fentanyl infusion	None mentioned

Table 2. Characteristics of included studies - continued

First author, year, country	Study design	Premedication
Lemyre B, 2004, Canada	Randomized study	SG: morphine CG: placebo
Oei J, 2002, Australia	Randomized controlled non-blinded trial	SG: morphine, atropine, suxamethonium CG: none
Buthada A, 2000, USA	Randomized placebo controlled non-blinded trial	SG: thiopental CG: placebo
Naulaers G, 1997, Belgium	Prospective observational	Methohexital

Abbreviations: CG, control group; GA; gestational age; SG, study group.

Table 3. Objective scoring systems

Level of sedation	Highest sedation	
Sedation score	4	3
Motor response to firm stimulus	No movements	Movement on firm stimulus
Definition	Effective sedation = score 3 or 4	
Relaxation score	4	3
Extremities tone	Hypotonic	Mildly hypotonic
Definition	Effective relaxation = score 3 or 4	
Good sedative state	-2	-1
Crying/irritability	No cry with painful stimuli	Moans or cries minimally with painful stimuli
Behavior state	No arousal to any stimuli, no spontaneous movement	Arouses minimally to stimuli, little spontaneous movement
Facial expression	Mouth is lax, no expression	Minimal expression with stimuli
Extremities tone	No grasp reflex, flaccid tone	Weak grasp reflex, decreased muscle tone
Vital signs	No variability with stimuli, hypoventilation or apnea	<1% variability from baseline, with stimuli
Definition	Good sedative state = total score on all 5 items -7 to -3	

Parameter for start intubation	Start intubation	Consequences insufficient sedation/relaxation
Time	1-2 min after preoxygenation	
Relaxation	At disappearance of muscle fasciculations and begin of muscle flaccidity	Up to 4 extra doses of suxamethonium
Time	1 min after infusion	
Sedation	No reaction to heel rubbing	None mentioned

Lowest sedation

	2 Movement on slight touch	1 Spontaneous movements
Effective sedation = score 3 or 4		
	2 Normal tone	1 Hypertonic
Effective relaxation = score 3 or 4		
0	1	2
No sedation/no pain signs	Irritable or crying at intervals, consolable	High-pitched or silent continuous cry, inconsolable
No sedation/no pain signs	Restless, squirming, awakens frequently	Arching, kicking, constantly awake or arouses minimally/ no movement (not sedated)
No sedation/no pain signs	Any pain expression intermittent	Any pain expression continual
No sedation/no pain signs	Intermittent clenched toes, fists, finger splay, body is not tense	Continual clenched fists, toes, finger splay, body is tense
No sedation/no pain signs	10-20% increase from baseline, SaO2 76-85% with stimulation – quick recovery	20% increase from baseline, SaO2 < 75% with stimulation, slow recovery
Good sedative state = total score on all 5 items -7 to -3		

Another scoring system is the relaxation score also used in the report of Smits et al., combining this score with the abovementioned sedation score. After the administration of propofol, level of sedation and muscle relaxation were determined. For relaxation, the muscle tone of the extremities was assessed (1 = hypertonic, 2 = normal tone, 3 = mildly hypotonic, 4 = hypotonic). Also, scores 3 and 4 reflect adequate relaxation. Both sedation and relaxation were assessed by the intubating neonatologist. Additional propofol was administered if sedation and relaxation were found unsatisfactory, until a satisfactory condition was achieved with no predefined maximum dose of propofol.[13] In the report of De Kort et al., in case of ineffective sedation, additional remifentanil was administered up to a predefined maximum, with a conversion to propofol in case of persisting inadequate sedation.[14]

The third score is from Thall et al., in their report describing how to perform dose-finding studies for premedication in neonatal intubation.[16] For this purpose they used the Neonatal Pain, Agitation and Sedation Scale (N-PASS) first described by Hummel et al.[30] The score consists of 5 variables that should all be scored within 5 minutes of the first sedative administration: crying/irritability, behavior state, facial expression, extremity tone, and vital parameters. Each item is scored on a 5-point scale from -2 to +2, with -2 corresponding to highest sedation and +2 corresponding to highest infant discomfort. For the purpose of endotracheal intubation, Thall et al. considered a score between -7 and -3 to reflect a good sedative state.[16]

DISCUSSION

This systematic review was performed to provide insight into the availability of validated objective scoring systems to assess newborn infants' level of sedation prior to intubation. The literature as per January 27, 2017 does not provide such a validated scoring system.

The decision to proceed with the intubation procedure after administering premedication should be based on the pre-intubation sedation level. However, studies reporting on this issue show that level of sedation is not always the key factor to proceed with intubation. In several studies, intubation was proceeded when a certain period of time had elapsed after the administration of premedication, assuming this amount of time being sufficient for drug effect. However, as drug pharmacokinetics and pharmacodynamics can differ considerably depending on gestational age and postnatal age, sufficient drug effect may need a different period of time in individual patients. Using the same time frame in all neonates may very well lead to a proportion of patients not being adequately sedated for the procedure. To guide individualized dosing, we strongly recommend basing the start of the intubation on the actual level of sedation and administering extra doses if necessary.

In the majority of studies included in this review, quality of sedation is indeed the key factor to guide intubation. However, this is assessed in very diverse ways, often rather subjective or not further specified. Validated scoring systems are lacking, especially prior to elective intubation in the operating room. However, the literature describes three objective assessment tools used in the NICU: the easy-to-perform sedation score first described by Naulaers et al., the also easy-to-perform relaxation score first used by Smits et al., and the more extensive scoring system suggested by Thall et al. which is based on the N-PASS described by Hummel et al.[13,14,16,30]

The purpose of validated objective scoring systems is to be able to predict effective sedation during the intubation procedure before actually starting the procedure, thereby preventing neonates from intubation without effective sedation. Validation of such scoring systems can be done by comparing the scoring system with the actual level of sedation during the intubation procedure in a larger group of patients. In neonatal intubation studies, the actual level of sedation during an intubation procedure is frequently assessed with the validated intubation score adopted from Viby-Mogensen et al.[31] In this intubation score, the items ease of laryngoscopy, position of the vocal cords, coughing, jaw relaxation, and movement of the extremities are all judged on a 4-point scale. A score of 2 or less on each item reflects effective sedation.

Although both using the Viby-Mogensen intubation score to qualify level of sedation during the intubation procedure, the reports of Smits et al. and De Kort et al. do not provide enough information to draw any conclusions about the accurateness of the sedation and relaxation scores. In the sedation score, the absence of a motor reaction or only a slight motor reaction to a firm stimulus is presumed to indicate the neonate will tolerate the insertion of the endotracheal tube into the supraglottic airway. However, in this assumption, the used stimulus should be stronger than the act of inserting an endotracheal tube. The question rises if the act of inserting an endotracheal tube, mainly via the nasal route, requires a stronger stimulus than heel rubbing. For example, by anesthesiologists, the much firmer stimulus of pinching the trapezius muscle is frequently used before inserting a supraglottic airway. Validation of that stimulus in a clinical study has not been reported. In summary, although both sedation and relaxation scores seem potentially useful scores in the neonatal population, validation of these scores is mandatory before further use.

The scoring system suggested by Thall et al. concerns a comprehensive and precise scoring system, which is likely to adequately reflect the level of sedation. Also, different definitions can be used in case of different needs of sedation level according to its purpose. However, to the best of our knowledge, clinical trials using this scoring system

are lacking. Therefore, any conclusion about its accuracy and usability is not possible and validation is needed before future use. Even if validated, the scoring system must prove its suitability in daily practice. In neonatal intubation, fast performance of the procedure is mandatory, especially when fast acting agents are used. The extensiveness of the score could possibly make it time consuming and therefore less suitable.

Despite the lack of validated objective scoring systems, several reports do have shown that premedication before neonatal intubation has become standard practice in the majority of neonatal units.[10,11,32-38] There is, however, much debate about which premedication or premedication regimen is best. Studies evaluating certain premedication strategies are mainly focusing on using one dosing strategy for the entire neonatal population. However, pharmacodynamics and pharmacokinetics are influenced by factors such as gestational age, postnatal age and morbidity. For example, Smits et al. found that neonates of different gestational ages needed different doses of propofol for adequate sedation.[13] Most important in our opinion is that the used premedication achieves effective sedation. It should also have a quick recovery to allow for fast extubation, and have no significant side effects. The search for the most suitable premedication strategy should be directed towards personalized medicine and focus on administering just enough premedication to achieve adequate sedation in the individual patient. For this purpose, a scoring system that adequately indicates the level of sedation is mandatory.

The work of field and the techniques used differ between pediatric anesthesiologists and neonatologists. For example, they have different drug choices, pursue different levels of anesthesia (deep vs superficial) and require different duration of sedation (hours vs minutes). However, the goals of administering premedication during induction in the operating room and before intubation in the NICU are comparable and in both situations the level of sedation should be objectively assessed before continuing the procedure. With his in mind, neonatologists and anesthesiologists can possibly share valuable knowledge in this area of the field. With the availability of a validated scoring system that can make a distinction between different levels of sedation, it should then be possible to use a single scoring system for both settings.

Limitation of this review is that we used the description of the intubation procedure in the methods section to answer the questions of our secondary objective. Because describing the entire procedure from administration of premedication to intubation was not the primary goal of the included studies, it is possible that these descriptions were not complete and that more scoring systems or other parameters were used in practice.

CONCLUSION

Validated scoring systems to assess the level of sedation prior to intubation in newborns are not available in the literature. Three objective sedation assessment tools seem promising but need further validation before they can be implemented into research and clinical settings. Future research is necessary to find a physical stimulus that enables clinicians to better anticipate the response to insertion of an endotracheal tube and laryngoscopy and to find the best premedication regimen to achieve the preset goals.

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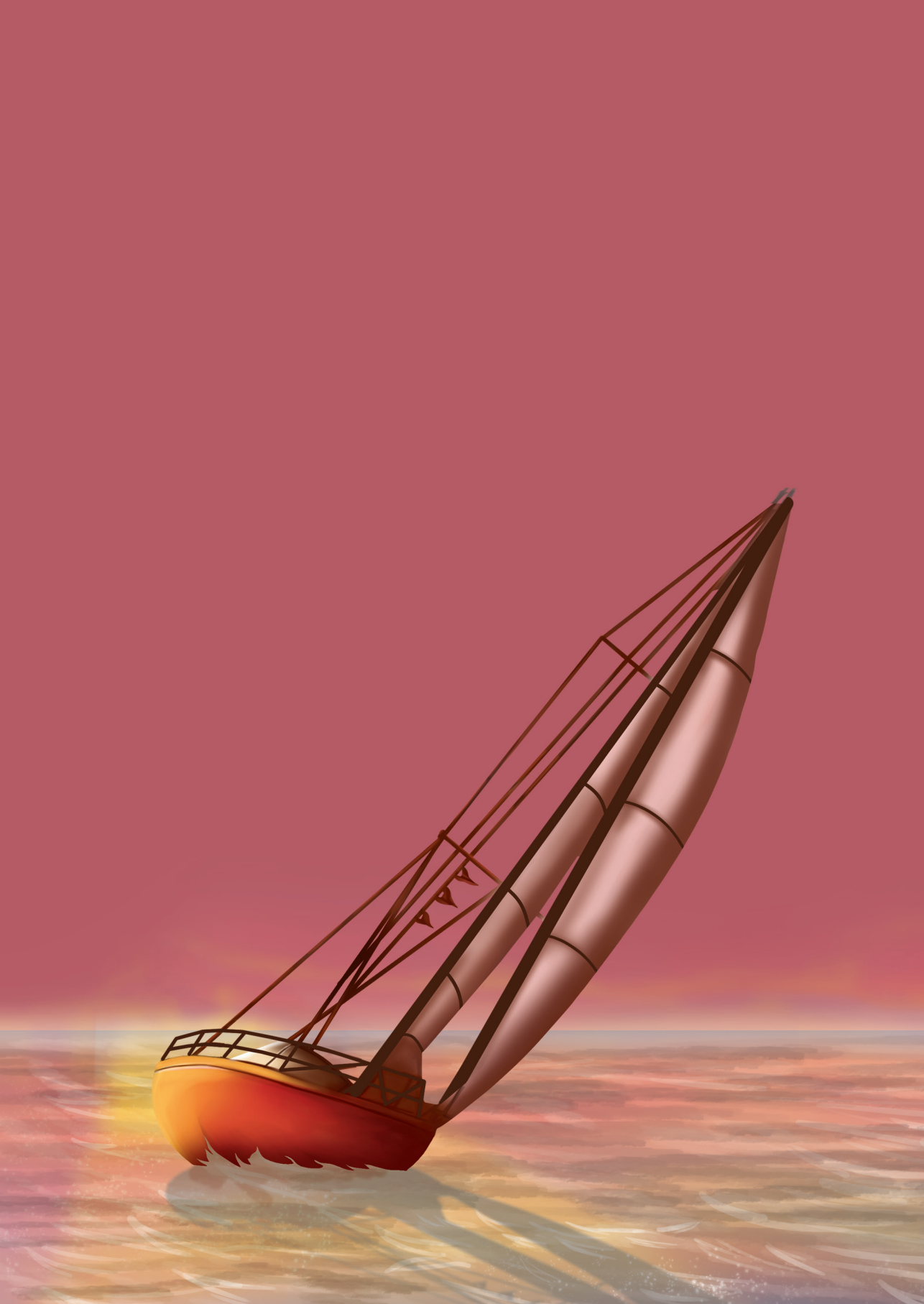

CHAPTER 6

EVALUATION OF AN INTUBATION READINESS SCORE TO ASSESS NEONATAL SEDATION BEFORE INTUBATION

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ABSTRACT

Background: Premedication for neonatal intubation facilitates the procedure and reduces stress and physiological disturbances. However, no validated scoring system to assess the effect of premedication prior to intubation is available.

Objective: To evaluate the usefulness of an Intubation Readiness Score (IRS) to assess the effect of premedication prior to intubation in newborn infants.

Methods: Two-center prospective study in neonates who needed endotracheal intubation. Intubation was performed using a standardized procedure with propofol 1-2 mg/kg as premedication. The level of sedation was assessed with the IRS by evaluating the motor response to a firm stimulus (1 = spontaneous movement; 2 = movement on slight touch; 3 = movement on firm stimulus; 4 = no movement). Intubation was proceeded if an adequate effect, defined as an IRS 3 or 4, was reached. IRS was related to the quality of intubation measured with the Viby-Mogensen intubation score.

Results: A total of 115 patients, with a median gestational age of 27.7 weeks (interquartile range 5.3) and a median birth weight of 1,005 g (interquartile range 940), were included. An adequate IRS was achieved in 105 patients, 89 (85%) of whom also had a good Viby-Mogensen intubation score and 16 (15%) had an inadequate Viby-Mogensen intubation score. The positive predictive value of the IRS was 85%.

Conclusions: Pre-intubation sedation assessment using the IRS can adequately predict optimal conditions during intubation in the majority of neonates. We suggest using the IRS in routine clinical care. Additional research combining the IRS with other parameters could further improve the predictability of adequate sedation during intubation.

INTRODUCTION

Endotracheal intubation is a frequently performed distressing procedure in the Neonatal Intensive Care Unit (NICU), and potentially complicated by a number of serious adverse physiological events.[1-7] Adequate sedation by the use of premedication before intubation may prevent these adverse events, reduces the duration and number of attempts needed for successful intubation, and prevents traumatic injury to the airway.[3,6-11] Routine use of premedication before (semi-)elective intubation has increased over the past decades.[12-18]

The main goal of premedication is to achieve an adequate level of sedation to facilitate the intubation procedure. Therefore, intubation should not be started until this level of sedation is achieved. However, there is no clear definition about the target level of sedation, and the assessment of sedation is often subjective and may vary between clinicians. The literature does not provide validated tools to assess the pre-intubation level of sedation.[19]

In their study to evaluate the effect of methohexital as premedication in neonatal intubation, Naulaers et al. described the effect of methohexital on sedation, relaxation, and sleep.[20] The level of sedation was assessed as the motor response to a firm stimulus (heel-rubbing) and four degrees of reactions were defined: "moves spontaneously," "moves when touched," "moves when stimulated," and "no reaction to stimulus." Relaxation was assessed by evaluating muscle tone in arms and legs, using four categories: "hypotonic," "mildly hypotonic," "normal tone," and "hypertonic." The degree of sleep was noted as "awake," "easily woken," and "deep asleep." The results of this study show that the level of sedation, degree of muscle relaxation, and degree of sleep correlate very well.[20] Therefore, we judged the motor reaction to a firm stimulus to be a very useful and easy-to-perform score to assess the pre-intubation level of sedation and named this score the Intubation Readiness Score (IRS). The aim of our study was to evaluate the suitability of this IRS in adequately indicating the pre-intubation sedation level by correlating the IRS to the quality of intubation. We hypothesized that the IRS performed after the administration of premedication would adequately predict Viby-Mogensen intubation scores during intubation.

METHODS

Study population

This prospective two-center study was performed in the level III NICUs of the Erasmus MC Sophia Children's Hospital, Rotterdam and Máxima Medical Center, Veldhoven, both in the Netherlands, between June 2015 and January 2017. Patients admitted to one of these NICUs were eligible for participation in this study if they needed (semi-) elective endotracheal intubation. The exclusion criterion was participation in other premedication studies at the same time. We used the NEAR4KIDS registry definitions regarding intubation encounters and attempts. An encounter is defined as one attempt of completed advanced airway management intervention including tracheal intubation. An attempt is defined as a single advanced airway maneuver beginning with the insertion of the laryngoscope into the patient's mouth and ending when the device is removed.[21] Because we allowed patients to be included in the analysis only once, we only included every first intubation attempt of every first intubation encounter per patient.

Procedure

Intubation was performed according to a standardized procedure. Propofol 1.0-2.0 mg/kg body weight was administered intravenously followed by a saline flush in 30 s. Immediately after propofol administration, IRS was assessed every 30 s by firmly rubbing the heel of the patients' foot and grading the motor reaction to this stimulus (Table 1). Applying this stimulus and judging the reaction was always done by one of the team members performing the intubation procedure. Both scores 3 and 4 were presumed to indicate adequate sedation for the intubation procedure. Therefore, when a score of 3 or 4 was reached, intubation was proceeded. If the IRS was still 1 or 2 after 3 min, an additional dose of propofol was administered, and again IRS was assessed every 30 s. This procedure was repeated until IRS 3 or 4 was reached. The time frame of 3 min before administering a new dose of medication was based on the known fast onset of action of propofol. Intubation was performed by pediatric residents, neonatal nurse specialists, fellows in neonatology, and neonatologists.

Table 1. Intubation Readiness Score

Score	Motor reaction to firm stimulus
1	Spontaneous movement
2	Movement in reaction to slight touch
3	Movement in reaction to firm stimulus
4	No movement

Outcome measures

The primary outcome of this study was the positive predictive value of IRS 3 and 4 in predicting good quality of intubation. The quality of the intubation was assessed with the standardized intubation score of Viby-Mogensen et al.[22] Scoring included rating of laryngoscopy, vocal cords, coughing, jaw relaxation, and limb movements. Each item was assigned a score of 1 to 4 (Table 2). Good quality of intubation was defined as a score ≤2 on each item. A score on one or more items of ≥3 implied inacceptable quality of intubation.

Table 2. Viby-Mogensen intubation score

Score	Laryngoscopy	Vocal cords	Coughing	Jaw relaxation	Limb movements
1	Easy	Open	None	Complete	None
2	Fair	Moving	Slight	Slight	Slight
3	Difficult	Closing	Moderate	Stiff	Moderate
4	Impossible	Closed	Severe	Rigid	Severe

Adequate intubation conditions were defined as a score ≤2 on each item

Data collection

Background characteristics as well as all IRS scores, data about all propofol doses, intubation conditions, and intubation attempts were collected on standardized intubation registration forms.

Statistical analysis

SPSS (IBM SPSS Statistics for Windows, version 22.0. Armonk, NY, USA) was used to analyze the data. Relevant patient data were reported as numbers with percentages for nominal variables and median and interquartile ranges (IQR) for continuous variables. Positive predictive values of IRS scores 3 and 4 combined as well as scores 3 and 4 separately, in predicting good quality of intubation, were determined (criterion validity). Univariate analysis was performed with Fisher's exact tests for categorical variables and the Mann-Whitney test for continuous variables. Two-tailed $p < 0.05$ was considered statistically significant.

Ethical approval

The IRS and Viby-Mogensen intubation score were implemented into daily practice as standard of care in both units because they potentially improved patient care. The study was judged as a prospective observational cohort study that did not incorporate extra risks or burden for the patients. Formal ethical approval to conduct the observational trial, according to the Dutch Law of Research with Humans, was not required (Medical Ethics Committee, Erasmus Medical Center, Rotterdam, the Netherlands, No. MEC-2017-240).

RESULTS

Study population

During the study period, 195 intubation encounters were performed in 164 patients. Only every first intubation attempt of every first intubation encounter was included, and therefore 164 intubation attempts were eligible for inclusion. Of these, 49 attempts (30%) were excluded because data regarding IRS and/or intubation scores were lacking or incomplete, leaving 115 intubation attempts eligible for analysis.

IRS and intubation conditions

IRS and intubation scores of the 115 patients that were eligible for analysis are shown in the flowchart in Figure 1. In 10 patients (9%), intubation was started despite an IRS of 1 or 2, thereby violating the standardized protocol. These patients were excluded from further analysis. IRS 3 or 4 was achieved in 105 patients (91%). Eighty-nine patients with IRS 3 or 4 had good quality of intubation, leading to a positive predictive value of 85%. IRS was 3 in 62 patients, of whom 56 patients had good quality of intubation, leading to a positive predictive value of 90%. IRS 4 was reached in 43 patients. Of these, 33 patients had good quality of intubation, leading to a positive predictive value of 77%.

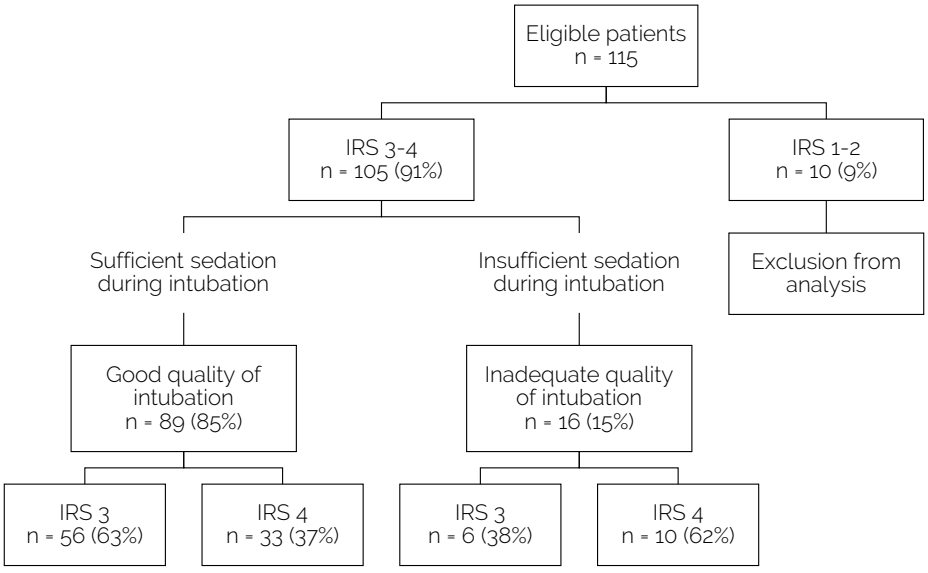

Figure 1. Flowchart of study patients

Table 3. Comparison of patient characteristics in patients with good and with inacceptable Viby-Mogensen intubation score after adequate IRS

	Good Viby-Mogensen intubation score (n = 89)	Inacceptable Viby-Mogensen intubation score (n = 16)	p value
Male gender, n (%)	51 (57)	10 (63)	0.79
Gestational age, weeks	27.7 (6.8)	27.5 (5.2)	0.51
Birth weight, g	995 (810)	1,110 (1,238)	0.71
Postnatal age, days	1 (4)	0.5 (1)	0.07
Weight at intubation, g	1,032 (783)	1,100 (1,238)	0.80
Cumulative dose of propofol, mg/kg body weight	2.0 (1.0)	2.0 (1.3)	0.29
Amount of propofol doses, n (%)	2 (1)	1.5 (1)	0.87
IRS 3, n (%)	56 (63)	6 (37.5)	0.10
Time between reaching good IRS and starting intubation, min	1 (2)	1 (2)	0.57

Data are median (interquartile ranges) unless otherwise indicated.

We performed a univariate analysis to search for factors that could explain why the IRS did not adequately predict the sedation level during intubation in 15% of our study population. The results of this analysis are shown in Table 3. This table shows that gender, gestational age, birth weight, postnatal age, weight at intubation, cumulative dose of propofol, amount of propofol doses, IRS being 3 or 4, and time in minutes between reaching good IRS and starting the intubation did not differ significantly between patients who had good Viby-Mogensen intubation scores and patients who had inacceptable Viby-Mogensen intubation scores. In 55 of the patients with good Viby-Mogensen intubation scores and in 6 patients with inacceptable Viby-Mogensen intubation scores, the function of the person who performed the intubation was registered. In patients with good Viby-Mogensen intubation scores, the intubation was performed by a pediatric resident in 13 patients (24%), a nurse specialist in 20 (36%), a neonatal fellow in 5 (9%), and a neonatologist in 17 patients (31%). In patients with inacceptable Viby-Mogensen intubation scores, intubation was performed by a pediatric resident in 3 patients (50%), a nurse specialist in 1 (17%), and a neonatologist in 2 patients (33%). These differences were not statistically significant (p = 0.28). The reason for intubation was reported for 87 patients with good Viby-Mogensen intubation scores and for 15 patients with inacceptable Viby-Mogensen intubation scores. Respiratory distress syndrome was the reason in 39 (45%) and 11 (73%) patients, respectively, and

respiratory insufficiency was the reason in 45 (52%) and 4 (27%) patients, respectively. Three patients with good Viby-Mogensen intubation scores were intubated for elective reasons versus none of the patients with inacceptable Viby-Mogensen intubation scores. Differences in reasons for intubation between both groups were not statistically significant (p = 0.116).

DISCUSSION

Premedication should be used for intubation in neonates whenever possible to minimize adverse physiological events, to reduce duration and number of attempts, to prevent traumatic injury to the airway, and to provide comfort. Accordingly, the intubation procedure should only be started when the given premedication has achieved a sufficient degree of sedation. However, validated objective scoring systems to assess the readiness for intubation are lacking.[19] This study aimed to evaluate the suitability of an IRS to assess if a newborn is ready for intubation after administration of premedication. We showed that this IRS can predict good quality of intubation in 85% of patients.

In the literature, no previous studies can be found that investigated the readiness for intubation. A recent systematic review shows only three potentially suitable scoring systems, all of them not validated.[19] One of these scores is the sedation score described by Naulaers et al. that we used to develop our IRS.[20] Another score to assess the level of sedation prior to intubation in neonates is the "good sedation state" from Thall et al.[23] This score is based on the Neonatal Pain, Agitation and Sedation Scale developed by Hummel et al.[24] and consists of 5 variables: crying/irritability, behavior state, facial expression, extremity tone, and vital parameters. Each item is scored on a 5-point scale from –2, corresponding to highest sedation, to +2, corresponding to highest infant discomfort. According to Thall et al., good sedation for endotracheal intubation is defined as a total score between –7 and –3.[23] To the best of our knowledge, further evaluation of this score has not been performed. Though this score might reflect the degree of sedation very accurately, it is an extensive and time consuming score that makes it less suitable to perform in a semi-acute situation. We have therefore chosen to further evaluate the sedation score of Naulaers et al.[20]

Adequate prediction of the quality of intubation in 85% of patients also means that in 15% of patients the IRS did not adequately predict the level of sedation during the intubation procedure. This might be explained by the fact that heel rubbing is a weaker stimulus than the introduction of the endotracheal tube into the nose or laryngoscopy. In this case, a stronger stimulus that better reflects the pain and stress of laryngoscopy and/or introducing the endotracheal tube into the nose should be used. However, introducing

a stronger, repetitive stimulus, to evaluate the level of sedation, thereby repeatedly exposing neonates to painful stimuli, is considered unethical. Another explanation for inadequate prediction of the level of sedation by IRS could be the short period of action of propofol. This pharmacological characteristic can cause the medication effect to be already expired at the moment the intubation is started, despite an IRS of 3 or 4 just before. This would mainly be the case in patients in whom a long period of time elapsed between reaching IRS 3 or 4 and starting the intubation attempt. However, statistical analysis revealed no significant difference in this time between patients with good and with inacceptable intubation conditions. We included only patients who received propofol as premedication. Future studies that use other sedative drugs are needed to further evaluate the IRS, which would increase the generalizability of our findings.

In our study, IRS 3 and IRS 4 were both hypothesized to predict sufficient sedation for the intubation procedure. Therefore, we combined both scores in our evaluation. Taking both scores apart, we expected that IRS 4 would better predict sufficient sedation during intubation than IRS 3. However, the results of our study show a nonsignificant higher positive predictive value of IRS 3 compared to IRS 4 (90% compared to 71%, respectively, p = 0.10). This could possibly be explained by the difference in patient numbers in both groups (56 vs. 33) or by the hypothesis that in patients with IRS 4 propofol has already reached its peak effect and by the time intubation is started, the effect is expired.

Though we belief that a positive predictive value of 85% makes the IRS certainly suitable for clinical practice, we should seek for methods to further improve this positive predictive value. It might be valuable to combine the motor reaction to heel rubbing with the degree of muscle relaxation. In the original report of Naulaers et al., the level of muscle relaxation was also scored on a 4-point scale (1 = hypertonia, 2 = normal muscle tone, 3 = mild hypotonia, 4 = profound hypotonia).[20] Adding this relaxation score to our IRS could possibly increase the number of patients in whom effective sedation can adequately be predicted before the intubation is started. Using both the sedation and the relaxation score was already done by Smits et al. studying propofol dosing in neonates.[25] They defined sufficient relaxation as mild or profound hypotonia. However, no conclusions about the usability of both scores can be drawn from their results.

In this study, we did not determine interrater variability of the IRS. This is an important limitation of this study. Where "spontaneous movements" and "no movement at all" are obvious scores and will most certainly not lead to much disagreement between clinicians, more disagreement could arise with the items "movement in reaction to touch" and "movement in reaction to a firm stimulus." Besides this, there could be variation in the meaning of the term "firm stimulus." Thus, interrater variability in IRS should be determined.

In conclusion, our study shows that by using the IRS, 85% of patients are adequately sedated for the procedure. Our protocol also enables the standardization of a highly complex procedure in vulnerable patients. We therefore advocate that the IRS should be used in every neonate who receives premedication prior to intubation. Further research combining the IRS with other parameters such as degree of muscle relaxation could increase the predictability of adequate intubation conditions even further.

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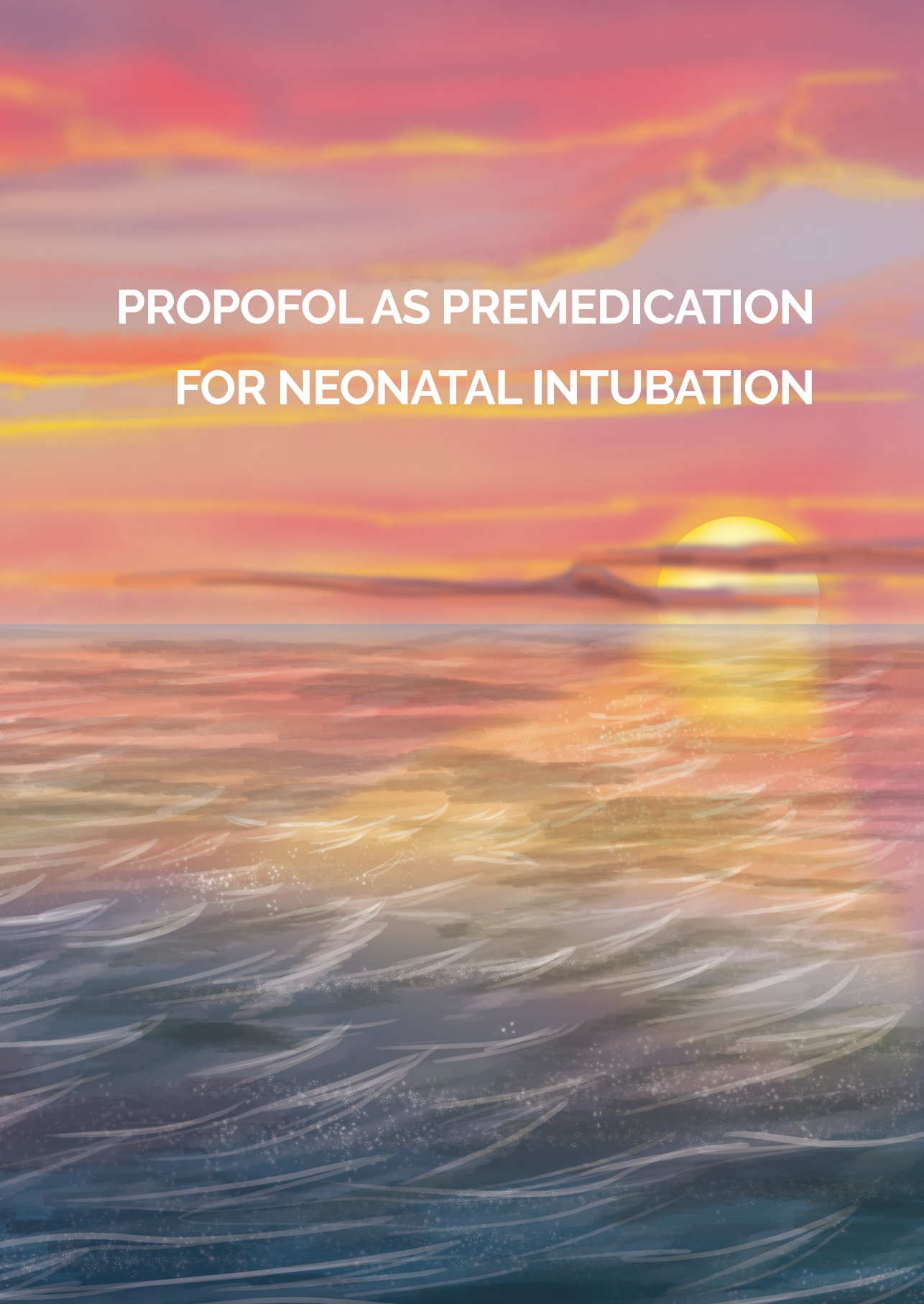
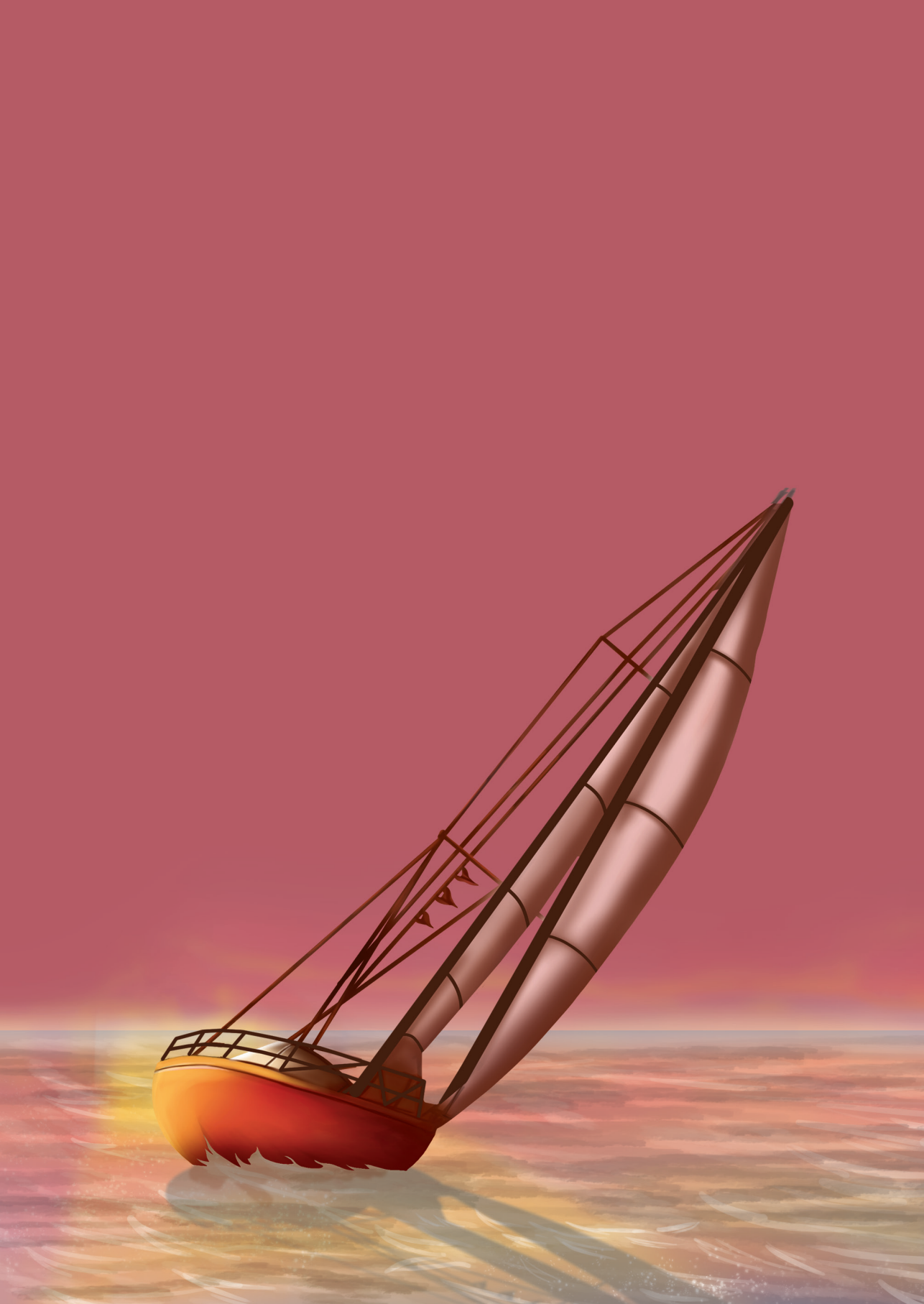

PROPOFOL AS PREMEDICATION
FOR NEONATAL INTUBATION



CHAPTER 7

PROPOFOL FOR ENDOTRACHEAL INTUBATION IN NEONATES: A DOSE-FINDING TRIAL

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ABSTRACT

Objective: To find propofol doses providing effective sedation without side effects in neonates of different gestational ages (GA) and postnatal ages (PNA).

Design and setting: Prospective multicenter dose-finding study in 3 neonatal intensive care units.

Patients: Neonates with a PNA less than 28 days requiring non-emergency endotracheal intubation.

Interventions: Neonates were stratified into 8 groups based on GA and PNA. The first 5 neonates in every group received a dose of 1.0 mg/kg propofol. Based on sedative effect and side effects, the dose was increased or decreased in the next 5 patients until the optimal dose was found.

Main outcome measures: The primary outcome was the optimal single propofol starting dose that provides effective sedation without side effects in each age group.

Results: After inclusion of 91 patients, the study was prematurely terminated because the primary outcome was only reached in 13% of patients. Dose-finding was completed in 2 groups, but no optimal propofol dose was found. Effective sedation without side effects was achieved more often after a starting dose of 2.0 mg/kg (28%) than after 1.0 mg/kg (3%) and 1.5 mg/kg (9%). Propofol-induced hypotension occurred in 59% of patients. Logistic regression analysis showed that GA and PNA did not predict effective sedation or the occurrence of hypotension.

Conclusions: Effective sedation without side effects is difficult to achieve with propofol and the optimal dose in different age groups of neonates could not be determined. The sedative effect of propofol and the occurrence of hypotension are unpredictable and show large inter-individual variability in the neonatal population.

INTRODUCTION

As awake intubation has multiple harmful effects,[1–7] the routine use of premedication before non-emergency intubation in neonates has become standard of care.[8–11] However, there is insufficient knowledge and lack of consensus about the most effective and safe strategy. Propofol is considered one of the acceptable options, despite being off-label for use in newborns, gaps in knowledge regarding optimal dosing and concerns about safety.[12] Because of its rapid onset and recovery, and its ease of use, propofol as a sedative for endotracheal intubation has been implemented into clinical practice in several neonatal intensive care units (NICUs).[13-17] Previous trials have shown conflicting results on sedative effect and concerning effects on blood pressure.[16-19]

Used propofol starting doses range from 1.0 to 2.5 mg/kg, with cumulative doses ranging from 1.0 to 6.0 mg/kg for successful intubation.[15-19] Although gestational age (GA) and postnatal age (PNA) are important determinants of propofol pharmacokinetics,[20] fixed propofol starting doses are often used for the entire neonatal population regardless of GA and PNA. The Exploratory Propofol Dose-Finding Study in Neonates (NEOPROP) is the only available dose-finding study in newborns that recently determined the effective propofol dose in 50% of patients (EC_{50}) for three different GA groups. This study also showed a great decrease in mean arterial blood pressure and a 62% incidence of hypotension.[21]

It is crucial to find propofol doses that are safe and effective in the entire newborn population. Therefore, we performed the NEOPROP-2 trial, which aimed to find age-specific propofol starting doses that provide effective sedation without side effects in neonates.

METHODS

Study design and setting

A prospective multicenter dose-finding study was conducted at three level III NICUs in the Netherlands between July 2014 and January 2018. An interim analysis was planned after every 6 months of inclusion, by an independent data and safety monitoring committee. The parents of all included patients provided written informed consent.

Participants

Neonates were eligible if they had a PNA <28 days and required non-emergency endotracheal intubation. Exclusion criteria were major congenital anomalies or neurological disorders, upper airway anomalies, sedative or opioid administration in the

preceding 24 hours and previous inclusion in the trial. The use of propofol was left to the discretion of the attending physician. If the hemodynamic status was judged to be sufficiently stable to use propofol, the patient could be included. Patients were stratified into eight different groups by GA and PNA (Figure 1), based on expected variation in effect and propofol clearance.

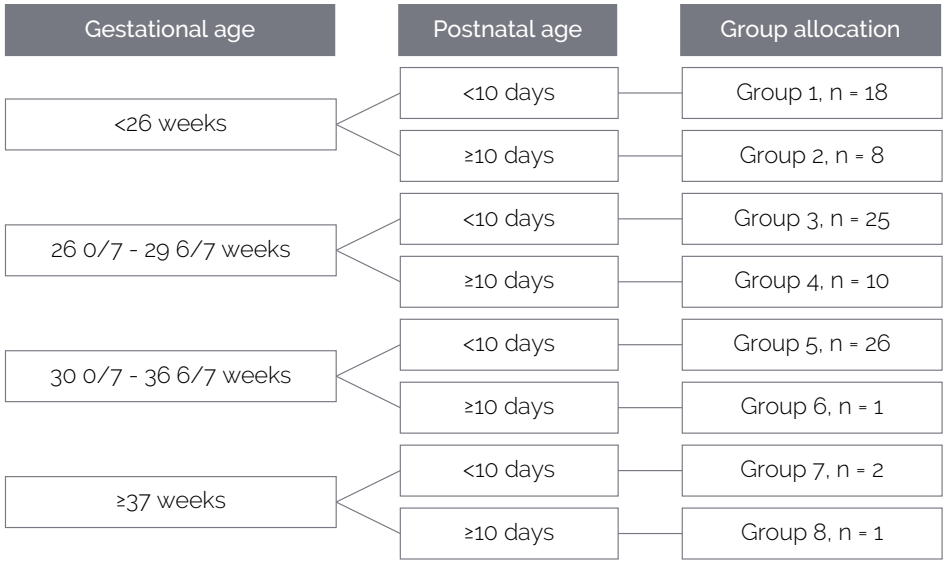

Figure 1. Group allocation

Interventions

Intubation procedure

Propofol was used as standard of care for endotracheal intubation in our units. Propofol (Fresenius Kabi, Schelle, Belgium) was administered as intravenous bolus followed by a saline flush for a total duration of 30 s. After propofol administration, the pre-intubation sedation level was assessed every 30 s up to 3 min after the infusion, using the Intubation Readiness Score (IRS).[22] When the pre-intubation sedation level was adequate, intubation was continued. In the case of insufficient sedation after 3 min, additional propofol was administered until sufficient sedation was reached. The amount of each additional propofol dose was left to the discretion of the attending physician. After intubation, the quality of intubation was measured by the Viby-Mogensen intubation score.[23] Data regarding propofol doses and intubation attempts were reported.

Dose-finding approach

A sample size of five patients per dose per group was used, based on the large inter-individual variability in effects of propofol that was found previously.[17] The first five patients in every group received a starting dose of 1.0 mg/kg propofol. Based on these five patients, the dose was increased or decreased with 0.5 mg/kg in the next five patients up to a maximum starting dose of 3.5 mg/kg because of expected toxicity. If needed for further optimization, a change of 0.25 mg/kg was applicable in the final dose-finding stage. Once the optimal propofol dose had been found, it was confirmed in another five patients. Dose-finding was completed per group when the optimal propofol dose was found, or when the maximum starting dose of 3.5 mg/kg was reached.

Primary outcome measures

The primary outcome of the study was the optimal single propofol starting dose for intubation in neonates with different GAs and PNAs, defined as the single starting dose that provided effective sedation without significant side effects. Effective sedation was determined with two variables that both needed to be adequate: pre-intubation sedation level and quality of intubation. Pre-intubation sedation level was determined with the IRS, and adequate pre-intubation sedation level was defined as IRS 3 or 4.[22] Quality of intubation was determined with the Viby-Mogensen intubation score.[23] Good quality of intubation was defined as a score of ≤2 on each of the five items.

Pre-defined side effects included hypotension, myoclonus, chest wall rigidity, persistent respiratory and/or circulatory failure, and bronchospasm. Blood pressure was measured invasively if an indwelling arterial catheter was present. Data were collected every minute from 5 min before until 30 min after the start of propofol administration, every 5 min from 30 to 60 min and every hour thereafter up to 24 hours. When no arterial catheter was present, blood pressure was measured non-invasively by an appropriately sized cuff every 5 min from 5 min before until 60 min after propofol administration and every hour thereafter until 24 hours. Propofol-induced hypotension was defined as a mean blood pressure (MBP) below postmenstrual age (PMA) detected in the first hour after propofol administration. Treatment of hypotension was left to the discretion of the treating physician.

For the primary outcome both effective sedation and absence of serious side effects needed to be positive. When either sedation was not effective or there were serious side effects, the primary outcome was not reached. Since both items needed to be positive, in case of one negative item and one missing item, the primary outcome was also not reached.

Secondary outcome measures

Secondary outcomes were the optimal propofol starting dose in the entire study population (regardless of age group), the need for additional doses of propofol and side effects in the entire study population and sedative effect and side effects in the most frequently used propofol starting doses. Finally, a logistic regression analysis was performed to find potential variables predicting the sedative effect and side effects after propofol.

Statistical analysis

The predefined sample size depended on which propofol dose was found to be adequate in five consecutive patients per group. Data were analyzed using SPSS (IBM SPSS Statistics for Windows, version 22.0. Armonk, NY, USA), and R 3.5 (R Core Team, Vienna, Austria). Patients were analyzed according to the intention-to-treat principle. Baseline characteristics were described by percentages for qualitative variables and median (interquartile range [IQR]) for quantitative variables. Comparison between dosing groups was performed with the Mann-Whitney U test for continuous variables and the Pearson's Chi square test or the Fisher's exact test, as appropriate, for categorical variables. Logistic regression analysis was performed to identify factors influencing the sedative effect and side effects of propofol with primary outcome, effective sedation, and hypotension as outcome variables. We analyzed the effects of gestational age (weeks), birth weight <10th percentile, male gender, postnatal age (hours), and propofol starting dose (mg/kg) on primary outcome and effective sedation. Total amount of propofol (mg/kg) was added as a confounder in the logistic regression analysis with hypotension as outcome variable. We used the Firth's method to reduce the bias in logistic regression that arises as a consequence of the relatively small sample size.[24,25]

RESULTS

Study population

The study population consisted of 91 patients (see Table 1). Three patients were included despite their PNA exceeding 28 days (two patients in group 2 [39 and 32 days] and one patient in group 4 [29 days]).

Study termination

An interim analysis after inclusion of 91 patients demonstrated a low inclusion rate in several groups and a 59% incidence of hypotension. In two age groups a propofol dose that provided effective sedation was found but caused hypotension in the majority of

patients. Therefore, an optimal dose as predefined in the primary outcome in these two groups was not established. The study was prematurely terminated, therefore, in consultation with the data safety monitoring committee.

Primary outcome

Dose-finding was only completed in groups 3 and 5, without finding an optimal propofol dose. The results of the dose-finding approach in sequential patients in groups 3 and 5 are presented in Figure 2. In both groups, starting doses of 1.0 and 1.5 mg/kg almost never led to effective sedation. A starting dose of 2.0 mg/kg led to effective sedation in many patients, but also led to a high incidence of hypotension, even after confirming this dose in another five patients per group. The dose, therefore, was decreased to 1.75 mg/kg, which did not provide effective sedation in the majority of patients in both groups.

Secondary outcomes

In the entire study population, effective sedation without side effects was achieved in only 12 patients (13%). Additional propofol was administered to 65 patients (71%) and the median cumulative propofol dose for successful intubation was 3.0 mg/kg (range 1.0 to 6.0 mg/kg, IQR 2.0-3.75).

Propofol starting doses of 1.0, 1.5 and 2.0 mg/kg were used in further in-depth analyses. There were no differences in patient characteristics between the three groups, with the exception of PNA (Table 2). This was lower in the 2.0 mg/kg dosing group, due to the higher inclusion numbers at younger postnatal ages. A starting dose of 2.0 mg/kg much more often led to effective sedation than starting doses of 1.0 and 1.5 mg/kg. The incidence of hypotension, however, was not different between the three starting doses.

Sufficient MBP data after propofol administration were available for 82 patients (90%). Propofol-induced hypotension occurred in 48 patients (59%). Of these, 26 patients (54%) were treated with volume resuscitation. Therapy with inotropes was started in nine patients (10%) at a median of 298 min after propofol administration (IQR 125-917 minutes). In seven of these patients, inotropes were started >2 hours after the start of propofol administration. In two other patients, inotropes were started within 2 hours and the hypotension is probably attributable to propofol. Comparison of MBP data before and after propofol was possible in 80 patients (88%). MBP decreased with a median of 34% (95% CI 36.5 to 29.1%) compared to baseline MBP. The lowest MBP was measured at a median of 21 min (95% CI 19.3 to 26.2 min).

Table 1. Patient characteristics

Characteristic	Entire population n = 91	Group 1 n = 18	Group 2 n = 8
Gestational age (wk), median (IQR)	27.7 (25.9-30.6)	25.3 (24.8-25.6)	24.8 (24.4-25.6)
Birth weight (gr), median (IQR)	1,045 (825-1,560)	720 (634-864)	740 (716-791)
Birth weight < 10th percentile, n (%)	23 (25)	5 (28)	0
Postnatal age (hr), median (IQR)	29 (9-213)	129 (38-173)	405 (384-681)
Actual weight (gr), median (IQR)	1,100 (830-1,560)	705 (643-838)	923 (825-1,084)
Male gender, n (%)	58 (64)	12 (67)	7 (88)
Reason for intubation, n (%)			
IRDS	44 (48.4)	2 (11.1)	0
Apnea	19 (20.9)	9 (50)	5 (62.5)
Sepsis/NEC	11 (12.1)	5 (27.8)	1 (12.5)
Respiratory insufficiency	13 (14.3)	1 (5.6)	2 (25)
Elective*	2 (2.2)	0	0
Other	2 (2.2)	1 (5.6)	0
Propofol starting dose, n (%)			
0.5 mg/kg	1 (1)	1 (6)	0
1.0 mg/kg	30 (33)	4 (22)	5 (63)
1.5 mg/kg	23 (25)	5 (28)	3 (37)
1.75 mg/kg	9 (10)	0	0
2.0 mg/kg	26 (29)	6 (33)	0
2.5 mg/kg	2 (2)	2 (11)	0

*Including prior to surgery or tube exchange. Abbreviations: IRDS, infant respiratory distress syndrome; IQR, interquartile range; NEC, necrotizing enterocolitis.

Group 3 n = 25	Group 4 n = 10	Group 5 n = 26	Group 6 n = 1	Group 7 n = 2	Group 8 n = 1
28.0 (26.9-28.9)	26.8 (26.3-27.1)	32.0 (30.4-33.6)	30.7	38.1	37.9
1,045 (890-1,223)	938 (886-1,076)	1,678 (1,480-2,129)	1,290	3,845	2,865
8 (32)	1 (10)	8 (31)	1 (100)	0	0
10 (6-31)	371 (307-524)	20 (5-26)	432	50	593
1,065 (910-1,193)	1,105 (925-1,123)	1,678 (1,460-2,125)	1400	3848	3100
13 (52)	6 (60)	16 (62)	1 (100)	2 (100)	1 (100)
17 (68)	0	23 (88.5)	0	2 (100)	0
2 (8)	3 (30)	0	0	0	0
3 (12)	1 (10)	1 (3.8)	0	0	0
3 (12)	4 (40)	2 (7.7)	0	0	1 (100)
0	1 (10)	0	1 (100)	0	0
0	1 (10)	0	0	0	0
0	0	0	0	0	0
5 (20)	6 (60)	6 (23)	1 (100)	2 (100)	1 (100)
5 (20)	4 (40)	6 (23)	0	0	0
5 (20)	0	4 (15)	0	0	0
10 (40)	0	10 (38)	0	0	0
0	0	0	0	0	0

Table 2. Patient characteristics and outcomes in 3 starting doses

	Dosing groups	
	1.0 mg/kg n = 30	1.5 mg/kg n = 23
Patient characteristics		
Gestational age (wk), median (IQR)	27.5 (25.86-30.93)	26.86 (25.57-30.14)
Birth weight (gr), median (IQR)	1,075 (784-1,410)	908 (780-1,600)
Postnatal age (hr), median (IQR)	156 (12-397)	37.35 (21-387)
Male gender, n (%)	22 (73)	12 (52)
Propofol dosing		
Extra propofol administered, n (%)	25 (83)	20 (87)
Cumulative propofol dose (mg/kg), median (IQR)	3.0 (1.9-4.0)	3.4 (2.5-4.5)
Primary outcome		
No. of patients with data available	30 (100)˙	23 (100)ǂ
Effective sedation without side-effects, n (%)	1 (3)	2 (9)
Sedative effect of propofol		
Adequate pre-intubation sedation level, n (%)	7 (23)	7 (30)
Quality of intubation		
No. of patients with data available	3 (10)	7 (30)
Good quality of intubation	1 (33)	3 (43)
Effective sedation		
No. of patients with data available	28 (93)	23 (100)
Effective sedation, n (%)	1 (4)	3 (13)
Hypotension		
No. of patients with data available	24 (80)	21 (91)
Occurrence of hypotension, n (%)	15 (63)	11 (52)
Volume resuscitation, n (% of hypotensive patients)	7 (47)	4 (36)

˙Both patients with missing data on effective sedation had side effects and all six patients with missing data on side effects had insufficient sedation. Therefore, a conclusion on the primary outcome could be drawn for all 30 patients. ǂBoth patients with missing data on side effects had inadequate sedation and, therefore, a conclusion on the primary outcome could be drawn on all 23 patients. ǂIn four patients with missing data on effective sedation, side effects were present and in only one patient both data on effective sedation and side effects were missing. Therefore, a conclusion on the primary outcome could be drawn in 25 out of 26 patients.

Dosing groups	Comparison between groups (p-values)		
2.0 mg/kg n = 26	1.0 vs 1.5	1.0 vs 2.0	1.5 vs 2.0
29.07 (26.43-31.71)	0.37	0.66	0.20
1,215 (895-1,568)	0.46	0.51	0.19
19.58 (8-43)	0.68	0.01	0.04
18 (69)	0.16	0.77	0.25
11 (42)	1.0	0.002	0.002
2.0 (2.0-3.0)	0.06	0.97	0.03
25 (96)ǂ			
7 (28)	0.57	0.02	0.15
24 (92)	0.75	<0.001	<0.001
19 (73)			
18 (95)	0.18	0.02	0.003
21 (81)			
18 (86)	0.21	<0.001	<0.001
26 (100)			
16 (62)	0.55	1.0	0.57
12 (75)	0.86	0.18	0.09

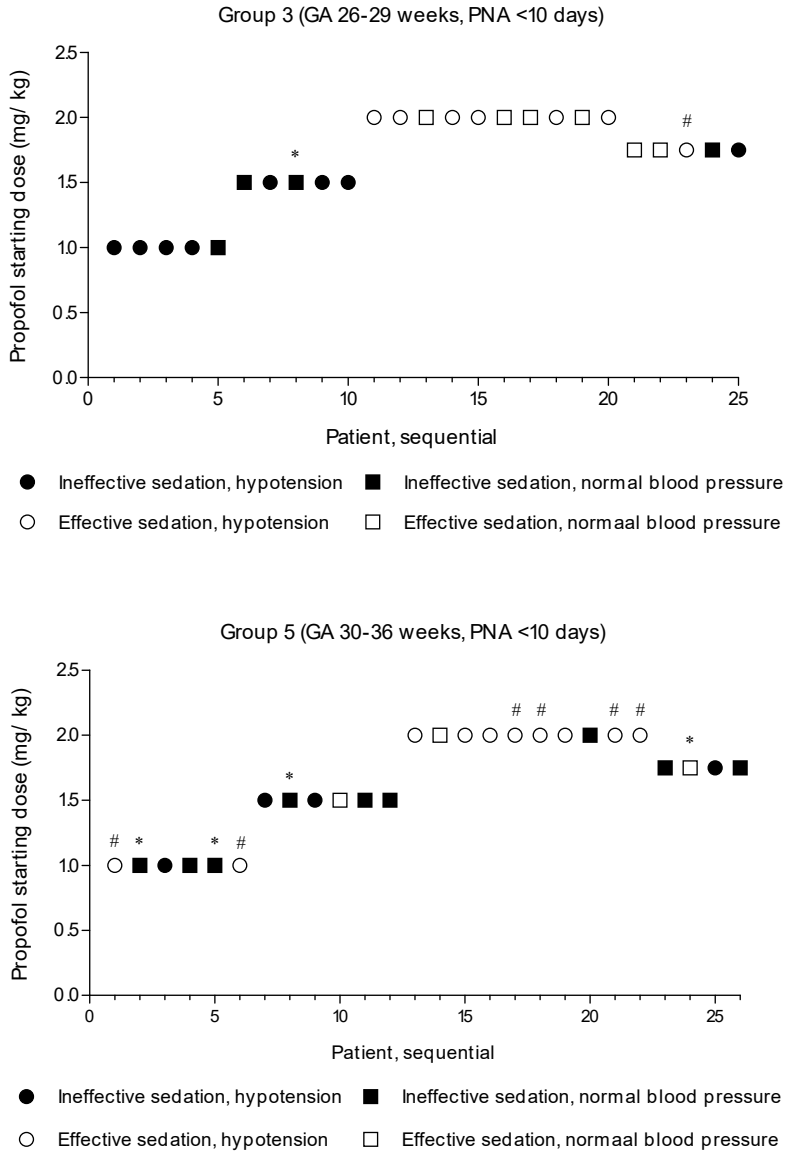

Figure 2. Dose-finding in groups 3 and 5

*Missing data on blood pressure, in the dose-finding approach considered to be normal in the absence of evidence of hypotension; # Missing data on intubation score, effective sedation only judged by pre-intubation sedation level. In group 5, the 1.0 and 1.5 mg/kg dosing subgroups both contain 6 instead of 5 patients. This was due to initial uncertainty of the suitability of the data for the primary outcome in 1 patient in both subgroups. An extra patient in both groups was included to ensure a total of 5 patient with viable data on the primary outcome. After re-evaluation, the data of all 6 patients in both subgroups turned out to be suitable.

Other side effects occurred in 10 patients (11%), including myoclonus in 8 patients (9%), bronchospasm in 1 patient (1%), and vocal cord spasm in 1 patient (1%). A total of 15 patients (16%) died at a median of 12 days after inclusion in this trial (range 0-57 days). Twelve patients died >72 hours after inclusion in the trial. One patient died from sepsis within 24 hours, and two patients died from necrotizing enterocolitis between 24 and 48 hours after inclusion. None were judged as directly attributable to the propofol administration.

The results of the logistic regression analysis (Table 3) showed that GA and PNA did not influence the effectiveness or safety of propofol.

Table 3. Logistic regression analysis with different outcome variables: primary outcome, effective sedation, and hypotension

	OR	95% CI	p-value
Primary outcome			
Gestational age (weeks)	0.94	0.77 - 1.15	0.54
Birth weight < 10th percentile (yes/no)	0.85	0.22 - 3.34	0.82
Male gender (yes/no)	1.72	0.46 - 6.40	0.42
Postnatal age (in hours)	1.00	0.99 - 1.00	0.69
Starting dose of propofol (mg/kg)	4.50	0.92 - 22.11	0.06
Effective sedation			
Gestational age (weeks)	1.00	0.80 - 1.23	0.98
Birth weight < 10th percentile (yes/no)	1.07	0.27 - 4.27	0.93
Male gender (yes/no)	2.67	0.76 - 9.36	0.13
Postnatal age (in hours)	1.00	0.99 - 1.00	0.65
Starting dose of propofol (mg/kg)	57.04	7.58 - 429.49	<0.001
Hypotension			
Gestational age (weeks)	1.09	0.94 - 1.26	0.26
Birth weight < 10th percentile (yes/no)	1.55	0.52 - 4.25	0.47
Male gender (yes/no)	0.94	0.36 - 2.45	0.90
Postnatal age (in hours)	1.00	0.99 - 1.00	0.45
Starting dose of propofol (mg/kg)	1.09	0.35 - 3.39	0.88
Cumulative dose of propofol (mg/kg)	0.74	0.48 - 1.14	0.18

Corrected by Firth's method to reduce bias because of relatively small sample size.

DISCUSSION

This dose-finding trial was designed to find the optimal single propofol dose for non-emergency endotracheal intubation providing effective sedation without significant side effects in neonates of different GAs and PNAs. To the best of our knowledge, this is the largest drug dose-finding study performed in the neonatal population. Unfortunately, dose finding could only be completed in two of the eight defined age groups without determination of the optimal propofol dose. Our results show a dose-dependent relationship for propofol to reach effective sedation. However, we also found the sedative effect to be unpredictable in the individual patient, and propofol is associated with a high incidence of hypotension. Based on these results, propofol might probably be not the most suitable premedication prior to endotracheal intubation in all neonates. In contrast to our results, Smits et al. were able to calculate specific propofol doses for preterm newborns in the first days of life that increased with GA.[21] Their suggested propofol doses were lower than the doses that resulted in adequate sedation in our study. This difference could be explained by different ways of analyses and outcome parameters in both studies. We did not calculate the EC_{50}, but showed that 2.0 mg/kg propofol starting dose is effective in 86% of patients.

The available literature shows conflicting results on the sedative effect of propofol. Doses of 1.0 and 2.5 mg/kg are found to provide sufficient sedation in some studies,[16,18] while other studies found insufficient sedation with doses of 1.0, 2.0 and 2.5 mg/kg.[17,19] These conflicting data underline that the sedative effect of propofol is difficult to predict. The indication for intubation could also play a role. For the Intubation-SURfactant-Extubation (INSURE) procedure, duration of sedation should be very short.[26] Therefore, clinicians might accept lower levels of sedation to diminish the risk of insufficient respiratory drive after the administration of surfactant and, therefore, the inability to immediately extubate the patient. However, regardless of the procedures that follow intubation, the act of laryngoscopy is equally stressful and equal levels of sedation should in our opinion be pursued.

GA and PNA are known covariates in propofol pharmacokinetics.[20] Therefore, we hypothesized that infants of different GAs and PNAs would need different propofol doses. Logistic regression analysis did not show a statistically significant effect of GA and PNA on the outcomes effective sedation and hypotension. Although unclear, the extended inter-individual variability in the effect of propofol seems much more important than GA and PNA in predicting the effect. Titrating propofol until the desired effect is achieved in the individual patient is probably the only way to ensure effective sedation in every patient. This, however, might still lead to a high incidence of hypotension.

Propofol is known for its pronounced effect on blood pressure in the neonatal population. We found a median decrease in MBP of 34%, which is in accordance with other studies.[16,17,21] The incidence of hypotension of 59% was comparable to that reported by Smits et al. (64%),[21] but much higher than found by Welzing et al. (38%).[16] This could be explained by the much smaller study sample, the lower dosages, and the different definition of hypotension.[16] Ghanta et al. did not report hypotension.[18] This could be explained by the possibility that MBP measurements were not continued long enough to detect hypotension, as hypotension appears at a median of 10-20 min after propofol.[16,17] Because of the pronounced effect that propofol can have on blood pressure, the hemodynamic status of the patient should be carefully evaluated before propofol is administered. In case of (impeding) hemodynamic compromise, other premedication with less pronounced effects on blood pressure should be considered.

Although blood pressure decrease after propofol is marked and there is a high incidence of hypotension, the implications for the short-term and long-term outcome are unclear. Blood pressure alone is a poor indicator of cardiovascular status.[27] In 95% of patients in the dose-finding study by Smits et al., cerebral autoregulation was intact during episodes of hypotension.[28] In the absence of clinical signs of shock, they labelled these episodes of hypotension as permissive.[21] Two other small studies on the cerebral effects of propofol in the neonatal population also showed no important correlation between blood pressure and cerebral oxygenation.[29,30] Although these findings are certainly reassuring, there is insufficient evidence on the short-term and long-term consequences of propofol-induced hypotension and blood pressure decrease to draw final conclusions. Until this is clarified in further studies, we should in our opinion be careful with designating propofol-induced hypotension and blood pressure decrease as permissive. On the other hand, the negative effects of propofol must be set against the negative effects of other premedication strategies. Almost all opioids, hypnotics and muscle relaxants also carry a risk of hypotension, and with fentanyl and remifentanil, there is also a risk of chest wall rigidity.[12]

Our study has several limitations. First, we were unable to perform dose-finding as planned because patient inclusion in several groups proved to be very difficult. Reasons were insufficient time for achieving parental consent, and the very low incidence of endotracheal intubation in the higher gestational age groups. Second, we used a very strict definition of hypotension. Even a single measurement of MBP below PMA in the first 60 min after propofol was marked as hypotension. It is questionable whether this single measurement of MBP below PMA has any clinical relevance. Adding a time element to the definition may better reflect the patients with clinically relevant hypotension. Unfortunately, we were unable to provide synchronized neuro-monitoring data, which

could have helped to study the clinical relevance of hypotension on cerebral oxygenation and perfusion in greater detail. Third, the treatment of hypotension was left to the discretion of the treating physician, which is likely to have caused variability between clinicians and between centers.

CONCLUSIONS

The results of this large dose-finding study suggest that in the neonatal population it is difficult to achieve effective sedation without the occurrence of significant side effects with a single propofol bolus. The effects and side effects of propofol in the neonatal population are highly variable and unpredictable. Propofol in the neonatal population should only be used after careful consideration in each individual patient and should be titrated based on the sedative effect with strict monitoring of blood pressure and hemodynamic status. As long as the ideal premedication strategy in the neonatal population has not been elucidated, the pros and cons of different strategies including propofol should be balanced against each other. A greater effort should be made to move forward from a one-strategy-fits-all idea towards personalized neonatal pharmacology.

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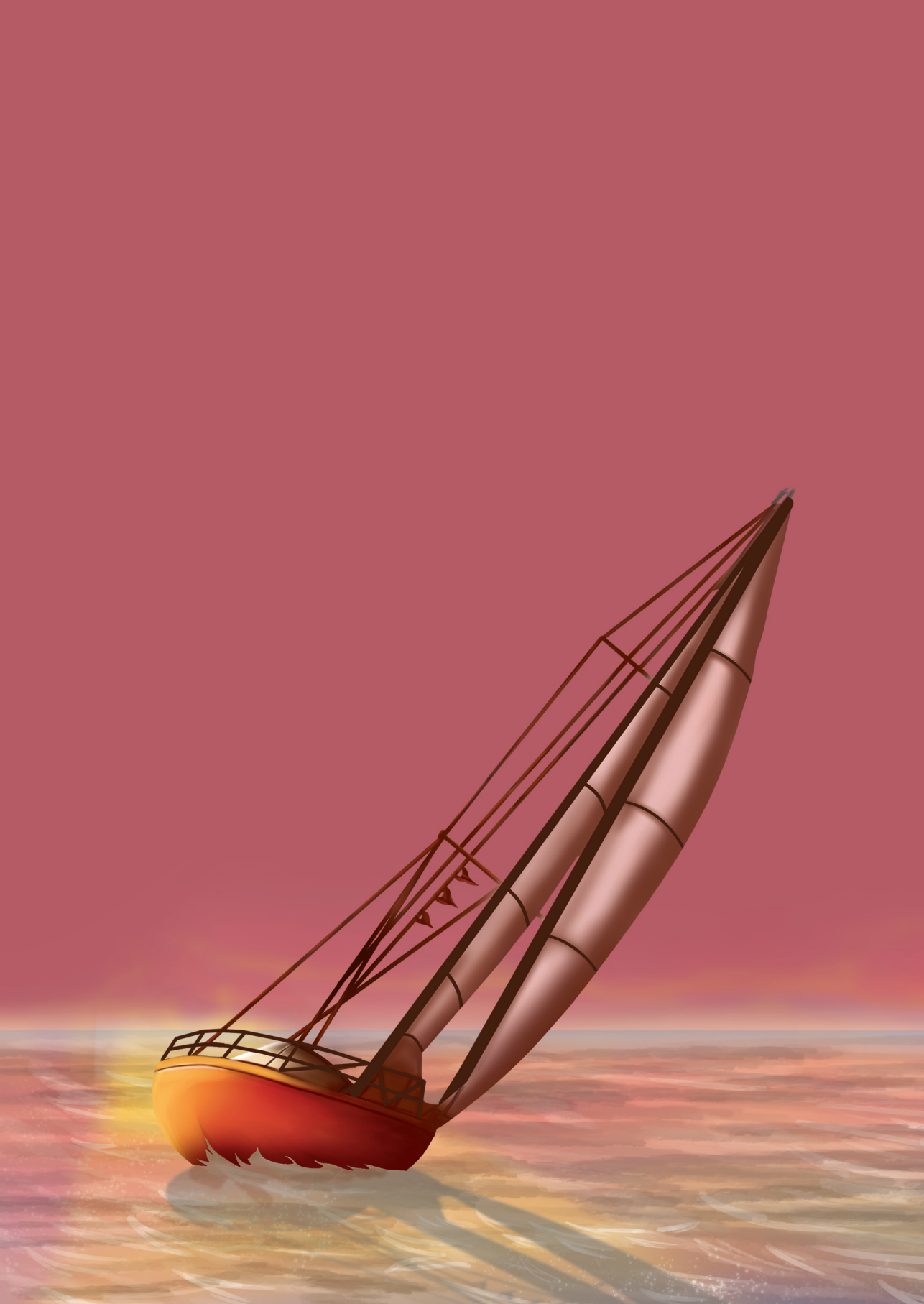

CHAPTER 8

PROPOFOL IN NEONATES CAUSES A DOSE-DEPENDENT PROFOUND AND PROTRACTED DECREASE IN BLOOD PRESSURE

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ABSTRACT

Aim: To analyze the effects of different propofol starting doses as premedication for endotracheal intubation on blood pressure in neonates.

Methods: Neonates who received propofol starting doses of 1.0 mg/kg (n = 30), 1.5 mg/kg (n = 23) or 2.0 mg/kg (n = 26) as part of a previously published dose-finding study were included in this analysis. Blood pressure in the 3 dosing groups was analyzed in the first 60 minutes after start of propofol.

Results: Blood pressure declined after the start of propofol in all 3 dosing groups and was not restored 60 minutes after the start of propofol. The decline in blood pressure was highest in the 2.0 mg/kg dosing group. Blood pressure decline was mainly dependent on the initial propofol starting dose rather than the cumulative propofol dose.

Conclusion: Propofol causes a dose-dependent profound and prolonged decrease in blood pressure. The use of propofol should be carefully considered. When using propofol, starting with a low dose and titrating according to sedative effect seems the safest strategy.

INTRODUCTION

It is known that awake endotracheal intubation in newborns causes multiple harmful effects.[1-3] Therefore, in 2001 consensus was reached that only in the delivery room and in life-threatening situations associated with the unavailability of intravenous access, tracheal intubation should be performed without the use of analgesia or sedation.[4] Almost twenty years later, the most effective and safe premedication strategy in the newborn population is still to be determined. Propofol is considered one of the acceptable options[5] and is shown to be very easy in use.[6] Therefore, propofol has been implemented into clinical practice.[7-11]

In the past decade, several studies have appeared reporting on the use of propofol for neonatal intubation, with somewhat conflicting results about the sedative effect related to dose.[6,9,10,12,13] Results regarding the hypotensive effect of propofol are probably even more conflicting, varying from no or only a slight decrease in blood pressure,[6,11] to a more pronounced decrease in blood pressure and a high incidence of hypotension.[9,10,13] Therefore, questions have been raised about the effectiveness and safety of propofol. In our recently performed propofol dose-finding trial (NEOPROP-2) we showed that propofol starting doses of 1.0 and 1.5 mg/kg were less effective in providing effective sedation compared to a propofol starting dose of 2.0 mg/kg. However, independent of the starting dose, propofol carried an unpredictable high risk of hypotension.[14]

The aim of the current study was to further analyze the effects of different propofol starting doses on blood pressure. With this in-depth analysis of the effects of propofol on blood pressure we aimed to provide guidelines for the use of propofol in clinical practice.

METHODS

Participants

Neonates from the previously published NEOPROP-2 trial were considered for inclusion.[14] The NEOPROP-2 trial was a prospective multicenter dose-finding trial conducted at three level III Neonatal Intensive Care Units in the Netherlands. Neonates with a postnatal age of less than 28 days who needed nonemergency endotracheal intubation were eligible for inclusion. Exclusion criteria were major congenital anomalies or neurologic disorders, upper airway anomalies, sedative or opioid administration in the preceding 24 hours and previous inclusion in the trial. Hemodynamic instability and underlying illnesses that are accompanied with a greater risk of hemodynamic instability were no specific exclusion criteria. The hemodynamic status and risk of hemodynamic insufficiency were

judged by the attending physician. If the attending physician judged the patient to be hemodynamically stable enough to receive propofol, the patient could be included in the trial. The study was registered at ClinicalTrials.gov (NCT02040909; EudraCT number 2013-005572-17) and approved by the local medical ethics committee (NL47607.078.14, MEC-2014-0.68). For further details concerning patient stratification, dose-finding approach and the assessment of effective sedation we refer to the initial publication.[14] In summary, dose-finding was performed by using a step-up-step-down approach, starting with a propofol dose of 1.0 mg/kg in five consecutive patients and adjusting the dose with steps of 0.5 mg/kg for the next five patients based on sedative effect and side effects of the previous dose. For this analysis, all patients from the NEOPROP-2 trial who received a propofol starting dose of 1.0, 1.5 and 2.0 mg/kg were included. Patients who received a different starting dose were excluded.

Blood pressure assessment

Blood pressure was measured invasively if an indwelling arterial catheter was present. Data were collected every minute from 5 minutes before until 30 minutes after the start of propofol administration, every 5 minutes from 30 to 60 minutes and every hour thereafter up to 24 hours. When no arterial catheter was present, blood pressure was measured noninvasively by an appropriately sized cuff every 5 minutes from 5 minutes before until 60 minutes after propofol administration and every hour thereafter until 24 hours. Propofol-induced hypotension was defined as a mean blood pressure (MBP) below postmentrual age (PMA) detected in the first hour after propofol administration. Treatment of hypotension was left to the discretion of the treating physician.

Primary outcome measure

The primary outcome measure was the course of blood pressure over time in the first hour after start of propofol infusion relative to baseline blood pressure in three different initial propofol starting doses (1.0, 1.5 and 2.0 mg/kg). Blood pressure measured within 5 minutes before start of the propofol infusion was considered as baseline. Blood pressure data were obtained every 5 minutes from 5 minutes before to 60 minutes after the start of propofol infusion.

Secondary outcome measures

Since the hemodynamic status of the patient could influence the patients' tolerability for propofol, we evaluated the incidence of hypotension and the change in MBP after start of propofol relative to the baseline MBP in relation to the hemodynamic status of the patient. For this purpose we included all patients in whom sufficient information regarding baseline MBP and MBP in the first hour after propofol was available, and divided these patients into three groups: group 1, hemodynamically stable patients (no

baseline hypotension and no sepsis/NEC); group 2, patients with baseline hypotension; and group 3, patients with a high risk of hemodynamic failure because of sepsis or NEC as indication for intubation. To elucidate the influence of cumulative propofol doses on blood pressure, we also performed a secondary analysis into the maximum decrease in MBP after different cumulative propofol doses.

Statistical analysis

Data analysis was performed using SPSS (IBM SPSS Statistics for Windows, version 22.0. Armonk, NY, USA) and Stata (Stata, version 15, StataCorp LLC, TX, USA). Baseline characteristics were described by numbers and percentages for qualitative variables and median and interquartile range (IQR) for quantitative variables. Comparison between groups was performed with the Mann-Whitney U test for continuous variables and the Fisher's exact test for categorical variables. Development of MBP over time-epochs was expressed as absolute change compared to baseline. Comparison of MBP development between groups was determined using a linear mixed model analysis to take into account the dependency of observations within patients. The linear mixed models included time (added to the model as a categorical variable represented by dummy variables), dose group and the interaction between time and dose group. Besides a crude analysis, also analyses adjusted for volume resuscitation and the administration of additional doses of propofol were performed. This was done by adding volume resuscitation and the administration of additional doses of propofol to the linear mixed models as time-dependent covariates. In addition, a linear mixed model analysis was performed with the cumulative dose of propofol as independent variable and the repeatedly measured MBP values as outcome.

RESULTS

Study population

Of the 91 patients in the NEOPROP-2 study, 79 patients received a starting dose of either 1.0, 1.5 or 2.0 mg/kg of propofol and were included in this analysis. Median gestational age was 27.71 weeks (IQR 25.86-30.71), median birth weight was 1,065 grams (IQR 860-1,560) and the median postnatal age at intubation was 33.53 hours (IQR 8.37-279.53). Fifty-two patients (66%) were boys and 18 patients (23%) had a birth weight below the 10th percentile. Thirty patients (38%) received a propofol starting dose of 1.0 mg/kg, 23 patients (29%) received a propofol starting dose of 1.5 mg/kg and 26 patients (33%) received a propofol starting dose of 2.0 mg/kg. Patient characteristics, sedative effect of propofol and need for extra propofol doses in these three dosing groups are presented in detail in the initial publication.[14] A summary of these findings relevant to the purpose of this analysis is presented in Table 1.

Table 1. Patient characteristics and sedative effect in 3 different propofol starting doses (see original report[14] for details)

	Dosing groups
	1.0 mg/kg n = 30
Gestational age (wk), median (IQR)	27.5 (25.86-30.93)
Birthweight (g), median (IQR)	1,075 (784-1,410)
Postnatal age (h), median (IQR)	156 (12-397)
Male gender, n (%)	22 (73)
Reason for intubation, n (%)	
RDS	12 (40)
Apnea	6 (20)
Sepsis/NEC	4 (13.3)
Respiratory insufficiency	7 (23.3)
Elective	1 (3.3)
Other	0
Effective sedation, n (%)	1/28 (4)
Extra propofol administered, n (%)	25 (83)
Cumulative propofol dose (mg/kg), median (IQR)	3.0 (1.9-4.0)

Abbreviations: IQR, interquartile range; NEC, necrotising enterocolitis; RDS, respiratory distress syndrome.

Primary outcome measure

Occurrence of hypotension and lowest MBP in three dosing groups

In Table 2 data on MPB before administration of propofol, the definition of hypotension, and data on MBP after start of propofol in the three dosing groups are presented. These data show that the incidence of hypotension was not significantly different between the three groups. In the 2.0 mg/kg group more patients were treated with volume resuscitation (75%) compared to the 1.0 mg/kg (47%) and 1.5 mg/kg (36%) groups, but this difference did not reach statistical significance. The maximum decrease in MBP as percentage from baseline was equal in all three groups. However, this maximum decrease was reached significantly earlier in the 1.0 mg/kg group (18.2 minutes) compared to the 2.0 mg/kg group (28.6 minutes; p = 0.03).

Dosing groups		Comparison between groups (p-values)		
1.5 mg/kg n = 23	2.0 mg/kg n = 26	1.0 vs 1.5	1.0 vs 2.0	1.5 vs 2.0
26.86 (25.57-30.14)	29.07 (26.43-31.71)	0.37	0.66	0.20
908 (780-1,600)	1,215 (895-1,568)	0.46	0.51	0.19
37.35 (21-387)	19.58 (8-43)	0.68	0.01	0.04
12 (52)	18 (69)	0.16	0.77	0.25
		0.53	0.27	0.35
8 (34.8)	17 (65.4)			
8 (34.8)	4 (15.4)			
3 (13)	2 (7.7)			
2 (8.7)	2 (7.7)			
1 (4.3)	0			
1 (4.3)	1 (3.8)			
3/23 (13)	18/24 (86)	0.21	<0.001	<0.001
20 (87)	11 (42)	1.0	0.002	0.002
3.4 (2.5-4.5)	2.0 (2.0-3.0)	0.06	0.97	0.03

Absolute changes in MBP after propofol in the 3 dosing groups

The absolute changes in blood pressure compared to baseline at different time intervals after the start of propofol infusion for the three dosing groups are presented in Figure 1. These data show that MBP declined in all three groups compared to baseline, and that this decline was highest in the 2.0 mg/kg dosing group. In the 1.0 mg/kg group the decline in MBP from baseline was significant at 20, 25, 35 and 45 minutes after start of propofol administration. In the 1.5 mg/kg group the decline from baseline was significant at time points 5 up to and including 30 minutes and 55 minutes after start of propofol. Finally, in the 2.0 mg/kg group the decline in baseline was significant at all time points with the exception of 5 minutes after the start of propofol. Correcting for volume resuscitation and the administration of extra doses of propofol did not alter the results from the initial analysis (Figure 2).

Table 2. Blood pressure data in 3 different dosing groups

	Dosing groups
	1.0 mg/kg n = 30
Baseline MBP (mmHg), mean (SD)	40 (11.2)
Hypotension before propofol, n (%)	4/29 (14)
Hypotension at any time point after start of propofol, n (%)	15/24 (63)
Treatment of hypotension with volume resuscitation, n (%)	7/15 (47)
Lowest MBP (mmHg) after start of propofol, mean (SD)	28 (9.5)
Time after start of propfol (min) of lowest MBP, mean (SD)	18.2 (12.5)
Maximum decrease in MBP as % from baseline, mean (SD)	-30 (16.5)

Abbreviations: MBP, mean blood pressure; SD, standard deviation.

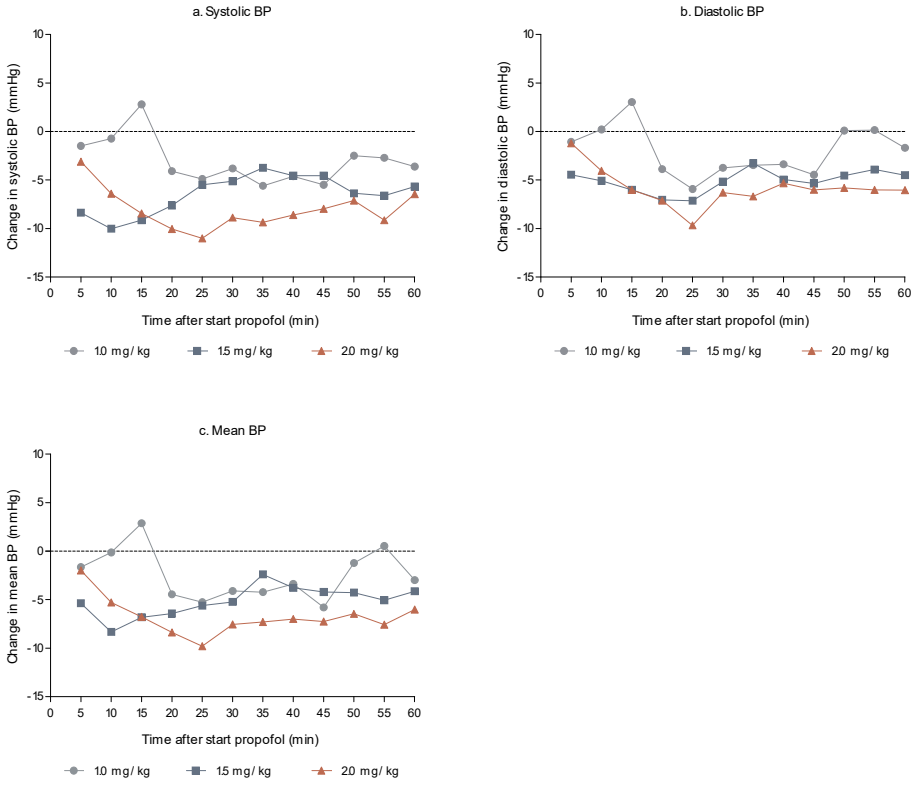

Figure 1. Changes of systolic, diastolic and mean blood pressure after start of propofol in 3 dosing groups

		Comparison between groups (p-values)		
1.5 mg/kg n = 23	2.0 mg/kg n = 26	1.0 vs 1.5	1.0 vs 2.0	1.5 vs 2.0
43 (9.7)	42 (12.3)	0.22	0.73	0.30
0/21	3 (12)	0.13	1.0	0.24
11/21 (52)	16/26 (62)	0.56	1.0	0.57
4/11 (36)	12/16 (75)	0.70	0.15	0.06
28 (6.9)	27 (5.5)	0.85	0.73	0.88
22.4 (14.3)	28.6 (18.2)	0.24	0.04	0.25
-36.4 (14.0)	-32.6 (18.7)	0.07	0.15	0.73

Table 3. Analysis of blood pressure in relation to hemodynamic stability

	Group 1 n = 53	Group 2 n = 7	Group 3 n = 9	P -value
Propofol starting dose, n (%)				
1.0 mg/kg	16 (30.2)	4 (57.1)	4 (44.4)	
1.5 mg/kg	16 (30.2)	0	3 (33.3)	
2.0 mg/kg	21 (39.6)	3 (42.9)	2 (22.2)	
Baseline MBP (mmHg), mean (SD)	44.5 (10.2)	25.3 (3.1)	42.7 (10.5)	<0.001
Absolute difference between baseline MBP and MBP indicating hypotension (mmHg), mean (SD)	15.0 (9.8)	-4.1 (4.0)	14.9 (9.8)	<0.001
Relative difference between baseline MBP and MBP indicating hypotension (%), mean (SD)	54 (35.9)	-13.6 (12.4)	53 (34.2)	<0.001
Hypotension at any time point after propofol administration, n (%)	28 (52.8)	7 (100)	6 (66.7)	0.05
Treatment of hypotension with volume resuscitation, n (%)	10/28 (36)	3/7 (43)	2/6 (33)	0.28
Lowest MBP (mmHg) after start of propofol, mean (SD)	28.5 (7.2)	20.9 (4.3)	27 (7.8)	0.01
Time after start of propofol (min) of lowest MBP, mean (SD)	23.5 (16.2)	19.9 (12.5)	24.8 (17.7)	0.88
Maximum decrease in MBP as % from baseline, mean (SD)	-34.3 (16.6)	-16.9 (16.1)	-35.9 (11.7)	0.05

Group 1 = hemodynamically stable (no baseline hypotension and no sepsis/NEC); group 2 = baseline hypotension; group 3 = high risk of hemodynamic failure based on sepsis or NEC as underlying morbidity. Abbreviations: MBP, mean blood pressure; NEC, necrotizing enterocolitis; SD, standard deviation.

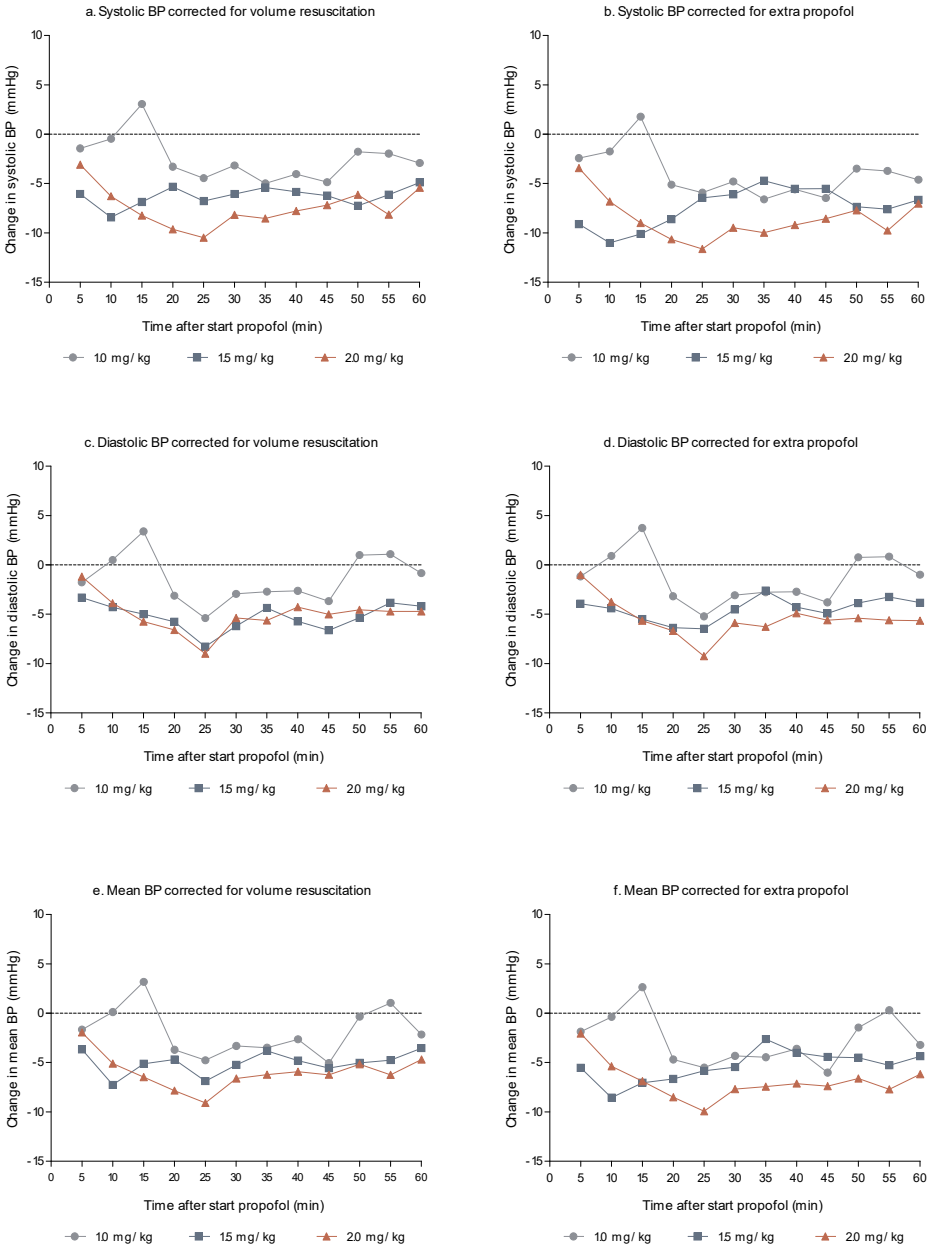

Figure 2. Changes in blood pressure after correcting for volume resuscitation and extra propofol administration

Secondary outcome measures

Changes in MBP in relation to hemodynamic status

For this analysis we included 69 patients of whom sufficient data regarding baseline MBP and MBP in the first hour after propofol were available. The results of the analysis are presented in Table 3. The incidence of hypotension was, as expected, significantly higher in group 2, and the lowest MBP after start of propofol was significantly lower in this group. The incidence of hypotension, the lowest MBP after start of propofol and the maximum decrease in MBP after propofol were equal between group 1 and group 3.

Changes in MBP in relation to cumulative propofol dose

Independent of the propofol starting doses that were administered, we also analyzed the average change in MBP over time for different cumulative doses of propofol, independent of the propofol starting dose. The results of this analysis are shown in Table 4. In all cumulative doses, MBP significantly declined compared to baseline, with the largest declines in the 1.0 and 2.5 mg/kg cumulative doses. These results have to be interpreted with some caution because of the small patient numbers, but could indicate that the cumulative dose of propofol did not influence the decline in MBP after propofol.

Table 4. MBP changes in different cumulative propofol doses

Cumulative propfol dose	Change in MBP relative to baseline	95% Confidence interval		p-value
1 mg/kg	-8.9	-12.8	-5.0	<0.001
1.5 mg/kg	-4.8	-8.8	-0.9	0.02
2 mg/kg	-2.8	-5.2	-0.4	0.02
2.5 mg/kg	-9.4	-14.7	-4.2	<0.001
3 mg/kg	-4.9	-7.6	-2.3	<0.001
≥ 3.5 mg/kg	-4.3	-6.7	-1.8	0.001

DISCUSSION

This post-hoc analysis was performed to explore the effects of different propofol starting doses as premedication for endotracheal intubation on blood pressure. The results of this analysis show that propofol starting doses of 1.0 mg/kg, 1.5 mg/kg and 2.0 mg/kg all caused a profound and prolonged decline in blood pressure. In all three dosing groups, MBP decreased by a maximum of 30%-35% in comparison with the baseline MBP, and MBP was not restored after one hour. The decrease in blood pressure was most pronounced with a propofol starting dose of 2.0 mg/kg.

The incidence of hypotension was over 50% in all groups. The blood pressure decline was mainly dependent on the starting dose that was used, and less influenced by the cumulative propofol dose that was administered to achieve successful endotracheal intubation.

To the best of our knowledge, this is the first study to evaluate the effect of different propofol doses on blood pressure. Comparison with data from the literature, therefore, is somewhat difficult. In our analysis, propofol-induced hypotension was observed in 63%, 52% and 62% of the patients receiving a propofol starting dose of 1.0 mg/kg, 1.5 mg/kg and 2.0 mg/kg, respectively. Previous literature shows somewhat controversial effects of propofol on blood pressure in newborns. Smits et al., in their dose-finding study, found an incidence of hypotension of 64% in the entire population irrespective of the starting dose that was administered.[13] Welzing et al. and Simons et al. both reported an incidence of propofol-induced hypotension of 39%.[9,10] In their randomized controlled trial comparing propofol to sufentanil and atracurium, Durrmeyer et al. found hypotension to occur in 13.3% of patients in the propofol group.[12] In contrast to these findings, others reported no hypotension to occur in their study population treated with propofol for endotracheal intubation.[6,11]

Part of these controversial results might be found in different definitions used for hypotension in preterm infants. Even in the 21st century, there is no generally accepted definition. Without any evidence to support it, the most popular criterion to define hypotension is mean blood pressure below gestational age.[15,16] The second most used definition is a MBP below the 10th or 5th percentile.[16] There are numerous reference ranges, often based on gestational age, birth weight and postnatal age criteria, with considerable variation among these reference ranges.[15,17] Finally, MBP below 30 mmHg is used to define hypotension, because some studies found loss of cerebral autoregulation below this threshold.[16,18,19]

In our study and in the study of Smits et al. the MBP below gestational age criterion was used. Both studies also used this definition for infants beyond the first 72 hours of life and therefore somewhat modified the definition to MPB below postmenstrual age.[13,14] Simons et al. also used the MBP below gestational age criterion but only reported on hypotension of a severity that required treatment.[9] This could explain why they found a lower incidence of hypotension of 39%. Should we have only reported on hypotension that required treatment, our incidence of hypotension would have been 32%. Welzing et al. used a much more liberal definition of MBP less than 25 mmHg in a study population with a gestational age of 29 to 32 weeks and 28 to 34 weeks respectively.[10] Should they have used the MBP below gestational age criterion, the incidence of hypotension would have been much higher.

Hypotension in the preterm infant has been associated with mortality, cerebral injury such as intraventricular hemorrhage and periventricular leukomalacia, and long-term neurologic sequelae.[16,20-24] The question rises, however, if every infant with low blood pressure needs treatment for hypotension. Blood pressure is only one aspect of cardiovascular status and may not directly correlate with tissue perfusion. Infants with hypotension in the absence of biochemical or clinical signs of shock presumably have adequate tissue oxygen delivery, a phenomenon indicated as permissive hypotension.[15] It has been shown that infants with permissive hypotension who did not receive treatment for hypotension had similar outcomes as normotensive patients.[25] A recent French population-based cohort study, however, showed that preterm infants below 29 weeks' gestation who were treated for hypotension in the first 72 hours of life had significantly higher survival rates without major morbidity and a lower rate of severe cerebral abnormalities, compared to infants with hypotension who were untreated.[26] These conflicting results indicate that the importance of hypotension in the preterm population is still to be elucidated.

Despite the statement that the hemodynamic status of the patients needed to be sufficiently stable to administer propofol, seven patients were hypotensive before the start of propofol. Besides this, nine patients received propofol while being at risk for hemodynamic insufficiency based on sepsis or NEC as underlying illness. Inclusion of these (possible) hemodynamically instable patients could have influenced the results and could have magnified the effect of propofol on blood pressure. Our analysis on the influence of hemodynamic status on the effect of propofol on blood pressure, however, shows that the effect of propofol on blood pressure is not different between patients who are presumed to be hemodynamically stable and patients who are presumed to have an increased risk of hemodynamic failure based on sepsis or NEC. Although caution with the interpretation of the results is warranted because of the small patient numbers, these data suggest that the tolerance for propofol in hemodynamically stable patients is not different from hemodynamically compromised patients. It should also be kept in mind that these results could also indicate that the hemodynamically stable patients in group 1 were not as hemodynamically stable as they were presumed to be.

In our initial analysis we showed that a propofol starting dose of 2.0 mg/kg provided effective sedation in 86% of patients, compared to 4% and 13% of the patients receiving a starting dose of 1.0 mg/kg or 1.5 mg/kg respectively.[14] Solely based on the sedative effect of propofol, a starting dose of 2.0 mg/kg of propofol would be the best strategy. However, despite an equal incidence of hypotension compared to the 1.0 mg/kg starting dose, a dose of 2.0 mg/kg had a much more profound decrease in blood

pressure despite a lower cumulative propofol dose compared to the 1.0 mg/kg group. Therefore, when using propofol as premedication for endotracheal intubation, the safest strategy seems to start with a low dose of 1.0 mg/kg and titrating until effective sedation has been reached.

The above-mentioned advice answers the question which propofol strategy for endotracheal intubation in preterm neonates is the safest. The question if this is safe enough and if it is justified to continue using propofol as premedication for endotracheal intubation in newborns still needs to be answered. The statement on hypotension without clinical and biochemical signs of poor perfusion being permissive, concerns the spontaneous course of blood pressure of extremely preterm infants in the first 72 hours.[17] Although most of the patients in our analysis were within their first 72 hours of life, the occurrence of hypotension was not spontaneous but induced by the administration of propofol. Although one third of patients in each of our 3 study groups did not fulfill our criteria of hypotension, MBP significantly decreased relative to baseline in almost all patients and this decrease was not restored 60 minutes after the start of propofol administration. Thewissen et al. showed that cerebral autoregulation stayed intact during episodes of hypotension caused by propofol.[27] Two other reports also could not demonstrate an important correlation between blood pressure and cerebral oxygenation in the neonatal population.[28,29] Although this finding is somewhat reassuring, the possible negative effects on short and long term outcomes of hypotension induced by the use of propofol are not known and possibly by far not as permissive as we might think. Neonatologists should ask themselves if they would expose the most vulnerable (extremely preterm) neonates to this side effect with unknown consequences on the short and on the long term. In our opinion the effect of propofol on blood pressure is a safety concern and the use of propofol should be carefully considered in every individual patient. Studies into the short term and long term effects of propofol-induced hypotension and comparison to alternative premedication strategies are warranted if propofol is continued to be used for this purpose in this population.

There are some limitations to our study. At first, not all patients in our study population had indwelling arterial catheters and therefore invasively and noninvasively measured blood pressure data were combined. Secondly, data of near infrared spectroscopy monitoring were missing on a large scale and consequently we have no data on cerebral oxygenation during propofol treatment.

CONCLUSION

Propofol used as premedication to sedate neonates for endotracheal intubation causes a profound and prolonged decrease in MBP which is more pronounced with a higher starting dose. It also causes a high incidence of propofol-induced hypotension, irrespective of the starting dose that is used. Although premedication for endotracheal intubation is essential, propofol might not be the preferred drug. When propofol is used in neonates, starting with a low dose and titrating according to sedative effect seems the safest strategy with the least pronounced effect on blood pressure.

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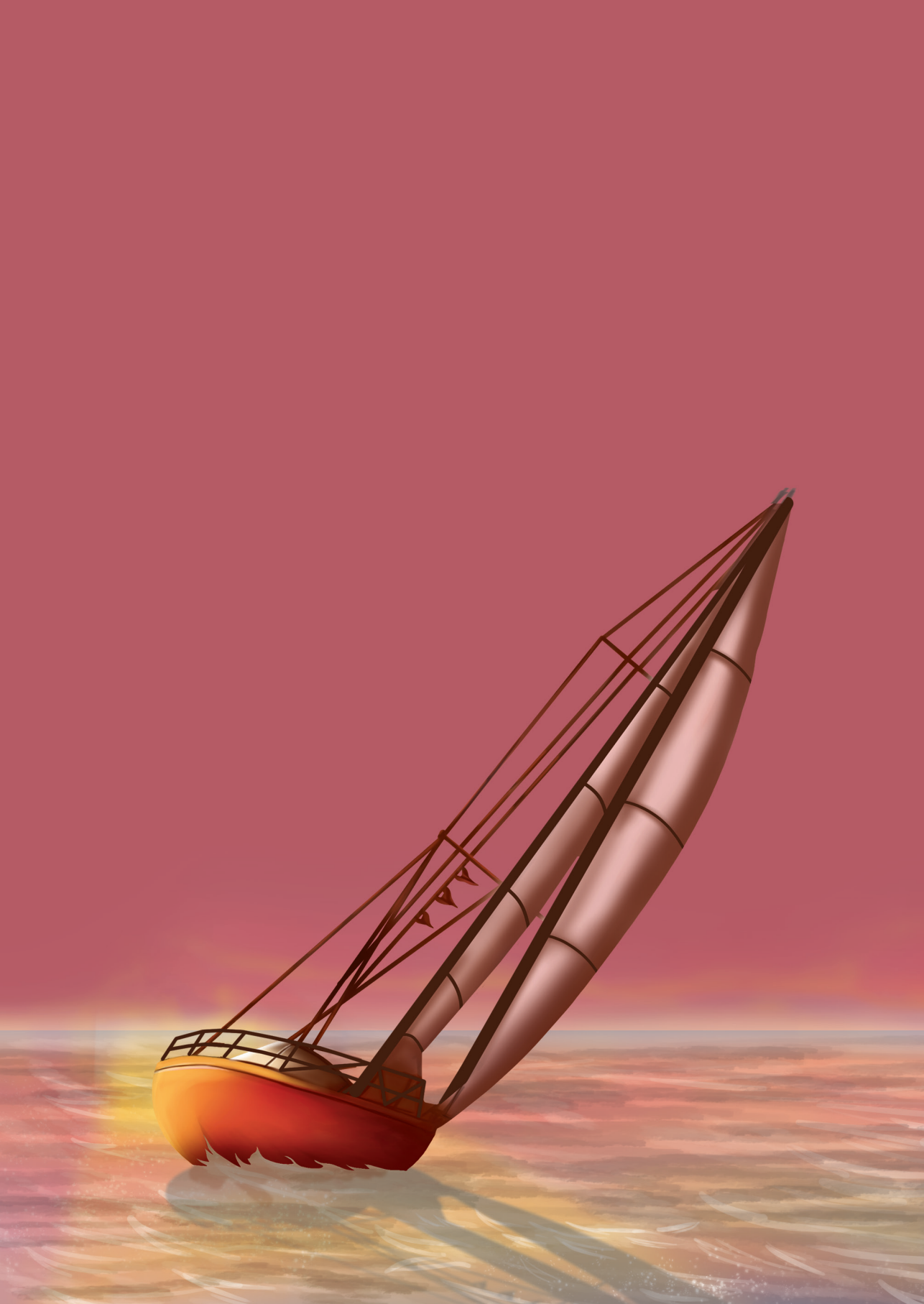
SUMMARY, CONCLUSIONS AND PERSPECTIVES



CHAPTER 9

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

GENERAL DISCUSSION

Endotracheal intubation in neonates is a frequently performed procedure that often requires multiple attempts for successful completion,[1-8] and is frequently accompanied by intubation related adverse events and severe oxygen desaturations.[1,6,9,10] This makes endotracheal intubation a high-risk procedure. Success and quality of neonatal endotracheal intubation can be influenced by several factors, including the physiological stability and airway anatomy of the patient, the use of suitable premedication and equipment, and the experience and competency of the health care giver.[11] Patient characteristics, such as the airway anatomy, physiological stability, underlying illness and reason for intubation, cannot be changed and can only be anticipated upon. Procedure characteristics such as the use of premedication, and the experience of the health care givers performing the procedure, however, can and should be influenced to pursue optimal success and the best quality of the procedure. In this context, we are "ready to tack". It is time for the available evidence, some of it already existing for years, to be implemented into clinical practice and to individualize the premedication strategy rather than using a population-based strategy, all to improve patient safety and to give optimal care during this high-risk procedure.

NEED FOR PREMEDICATION USE

The multiple intubation attempts that are often needed for successful intubation in neonates are not without consequences. Exposing neonates to multiple intubation attempts is associated with adverse events on the short as well as on the long term. Multiple intubation attempts are related to a higher frequency of intubation related adverse events and severe oxygen desaturations,[12] with each additional intubation attempt doubling the odds for these adverse events.[1,10] Besides this, multiple intubation attempts have been related to the occurrence of intraventricular hemorrhage. Sauer et al. showed that in preterm infants with a birth weight less than 750 gram, severe intraventricular hemorrhage was almost 28 times more likely to develop in infants who were exposed to 3 or more intubation attempts.[13] On the long term, multiple intubation attempts have been linked to neurodevelopmental impairment in preterm infants. Wallenstein et al. showed that the odds for developing neurodevelopmental impairment were almost doubled when exposed to multiple intubation attempts compared to successful intubation at the first attempt.[14] Both studies are limited by their retrospective nature, the relatively small sample size and the lack of information regarding illness severity of the included patients. Further research to elucidate a causal relationship between an increased number of intubation attempts, and intraventricular hemorrhage and neurodevelopmental impairment is necessary. The results, however, are enough to warrant caution exposing preterm infants to multiple intubation attempts.

The possibility of premedication decreasing the number of attempts needed for successful intubation has been known for several decades.[15-20] Recent studies have added evidence to this. Sawyer et al. demonstrated a relation between the use of sedatives or analgesics and paralytic premedication, and the number of intubation attempts.[12] Besides this, the use of paralytic premedication has been found to be independently associated with a decrease in the odds for intubation related adverse events.[1,9] This protective effect of paralytic premedication could not be confirmed by Hatch et al.[10] The frequency of paralytic premedication use in their study population, however, could have been too low to capture any beneficial effect. Added to the already existing evidence, the results of these recent studies again stress the need for appropriate premedication prior to endotracheal intubation. The results also suggest that the specific use of paralytic premedication could improve patient safety during the procedure.

The need for using premedication prior to endotracheal intubation is not new. The harmful effects of awake intubation and the possibility to reduce or eliminate these harmful effects by using premedication are known for decades.[15-18,20-24] Also the recommendation to use

premedication for nonemergency endotracheal intubations in neonates already exists about 20 years. Intubation without premedication should only be performed in the delivery room and in emergency situations when there is no intravenous access available.[25,26] Studies evaluating premedication use by asking clinicians about their premedication practices, showed that the routine use of premedication is about 90 to 100%.[27-30] Although these percentages are reassuring, the results of recent studies evaluating intubation practices in the NICU are alarming. The percentages of endotracheal intubations performed without premedication vary from 14% to as high as 38%.[1,2,9,10] These data might indicate that what clinicians say they do, is not always what they actually do in clinical practice.

Why was there such a high incidence of awake intubation in these studies? This question is difficult to answer, since all four abovementioned studies do not provide information regarding this issue. Intubations in the delivery room were not included in these studies and, therefore, to justify the absence of premedication according to the recommendation from 2001, it all should have been emergency intubations with no availability of intravenous access. Durrmeyer et al. previously showed that of all patients not receiving premedication before intubation, 85% did have an intravenous access at the time of intubation.[31] This indicates that there might be other reasons that keep neonatologists from administering premedication when intubating a neonate.

Several factors could play a role in a neonatologists' decision not to administer premedication, one of them being a risk for complications. However, serious complications after the administration of premedication before endotracheal intubation were not demonstrated by several randomized controlled trials.[32] In a multicenter observational study from France, Simon et al. showed that the rate of complications was not influenced by the use of premedication.[33] Insufficient evidence about efficacy and safety could be another reason for a neonatologist not to administer premedication.[34] Not only 20 years ago but even in the present time, premedication is less often used in smaller and younger neonates.[33,35,36] This apparent reluctance of neonatologists to administer premedication to extremely low birth weight infants could possibly be attributed to a greater concern about the side effects of premedication in these patients, or to the misconception that smaller and younger neonates would not need premedication. There is, however, no evidence that shows that extremely low birth weight infants have less adverse effects of awake intubation and experience less discomfort and pain. Just because these patients do not have the strength to struggle and fight the health care giver, does not mean they do not need premedication. Ozawa et al. also showed that premedication was less often used when surfactant administration and unstable hemodynamics were the intubation indications.[36] This could indicate concern for suppression of the respiratory drive and concerns for the effects of premedication on the patients' hemodynamic status.

Although these concerns are justified, awake intubation in these patients is probably not. Instead of not using premedication, the premedication strategy must be aligned with the indication for intubation and the underlying condition of the patient. In addition, the absence of guidelines for the use of premedication probably also plays a role. The presence of a clear local guideline regarding the use of premedication, also including types of drugs and dosages, could encourage neonatologists to use premedication. Finally, preparation times can be a factor withholding premedication use.[37] Studies have shown that preparation times can take up to 16 minutes.[38,39] This can be resolved by the use of pharmacy prepared prefilled syringes.

READY TO TACK – Towards improvement in the use of premedication

Recommendations for clinical practice

- Previous and recent evidence has sufficiently shown the harmful effects of awake intubation in neonates. The need for using premedication should no longer be questioned.
- There is no good reason to perform endotracheal intubation in awake neonates, except when it concerns an emergency situation in which the endotracheal tube should be placed without any delay.
- The unavailability of an intravenous access in itself should not be a contra-indication for the use of premedication. The possibility of stabilizing the patient with non-invasive ventilatory support or bag and mask ventilation to create time for providing an intravenous access should be considered.
- The harmful effects of awake intubation apply to all neonates, regardless of age, underlying illness and clinical condition. Therefore, these factors should be taken into account when choosing the most appropriate premedication strategy, but should not be an absolute reason to perform awake intubation.
- The use of premedication and the choice for a certain drug or combination of drugs should not be left at the discretion of the individual physician. Every neonatal unit should have a written guideline for the use of premedication in neonatal endotracheal intubation, which must describe specific premedication strategies for specific patient conditions. To eliminate preparation times, premedication should be readily available, for example in pharmacy prepared prefilled syringes.

Recommendations for future research

- To prevent the necessity of an intravenous access to administer premedication, future research should focus on the possibility of administering premedication via other routes, for example oral, nasal and buccal routes.

ASSESSMENT OF PREMEDICATION EFFECT

The administration of premedication is not a goal in itself. The aim of administering premedication is to provide an adequate level of sedation to provide comfort, minimalize pain, stress and physiological disturbances, and facilitate the procedure. Therefore, it is not only important to administer premedication but also to evaluate the effect and pursue an adequate sedation level before proceeding with the intubation procedure. In clinical practice, however, the level of sedation after the administration of premedication was often not assessed before intubation was started, or was assessed in a variable and subjective way. Objective validated scoring systems to assess the level of sedation in the neonatal population were not available. A literature search did, however, reveal three objective sedation assessment tools, which are all promising but need validation before they can be implemented into clinical practice.[40] We, therefore, developed an Intubation Readiness Score (IRS) to assess the level of sedation, that was based on the sedation score described by Naulaers et al.[41] Based on correlation of the IRS with the quality of intubation assessed by the intubation score of Viby-Mogensen,[42] the IRS was shown to accurately indicate the level of sedation during the intubation procedure in 85% of neonates.[43]

The IRS is currently the best available easy to perform tool to evaluate the effect of premedication. In 85% of patients the actual level of sedation is well predicted by the IRS. In 15% of patients, however, sedation during the intubation was inadequate even though the IRS indicated otherwise.[43] This stresses the need for further developing and expanding the IRS to improve its accurateness. It must, however, be ensured that the score does not become too extensive and time consuming for use in the acute situation of endotracheal intubation. A possibility would be to expand the IRS with the relaxation score, also described by Naulaers et al.[41] This score assesses the muscle tone of the extremities on a 4-point scale. Incorporating this relaxation score into the IRS, might improve its accurateness in assessing the level of sedation. Further studies have to be performed to validate this expanded IRS, by comparing the IRS with a gold standard for

assessing sedation level. As a gold standard for example the Viby-Mogensen intubation score can be used, as we did in our validation of the IRS.[42,43] In addition, heel rubbing as a tactile stimulus should be reconsidered. For certain patients, this stimulus might not be strong enough to reflect the pain and stress of laryngoscopy and introducing the endotracheal tube into the nostril. The use of a stronger stimulus, however, might raise ethical issues. Finally, the interobserver variability of the IRS has not been previously assessed. Since significant interobserver variation in the firmness of heel rubbing as well as the interpretation of the motor reaction following heel rubbing is possible, future research should address this issue.

READY TO TACK – Towards pursuing an adequate level of sedation

Recommendations for clinical practice

- After the administration of premedication, the level of sedation should be closely monitored by using objective scoring methods such as the Intubation Readiness Score.
- Intubation should only be performed when an adequate level of sedation is reached. Additional medication to achieve adequate sedation should be administered whenever needed.

Recommendations for future research

- Possibilities for expanding the Intubation Readiness Score to increase its positive predictive value for adequate sedation level should be investigated.
- The use of a stronger stimulus better reflecting the pain and discomfort that accompany the act of endotracheal intubation should be considered.
- The issue of interobserver variability in applying the firm stimulus and judging the motor reaction to that stimulus should be addressed.

THE USE OF DIFFERENT PREMEDICATION STRATEGIES

The effectivity of a premedication strategy that consists of a vagolytic, an analgesic and a muscle relaxant is supported by several studies. The atropine-opioid-muscle relaxant combination has been shown to have a higher first attempt success rate and, as a consequence, a lower total number of attempts, compared to the combination of atropine and an opioid without a muscle relaxant.[34,44,45] Roberts et al. also showed that

adding a muscle relaxant led to fewer and shorter oxygen desaturations.[34] Observational studies also showed a relatively high first attempt success rate and a high frequency of adequate intubating conditions.[46,47] More recent studies have shown that the use of paralytic medication in combination with a sedative or analgesic compared to a sedative or analgesic alone leads to fewer intubation attempts and a lower incidence of intubation related adverse events.[1,9,48] The use of an analgesic or sedative without a paralytic even led to more severe desaturations.[1,48] These results could indicate that the use of an analgesic or sedative alone is more harmful than awake intubation. These data, however, should be interpreted with caution. Of all patients treated with only an analgesic or a sedative in this study population, 35% were treated with morphine.[36] Because of its delayed onset of action, morphine is not a suitable candidate to be used as premedication.[49] The results do indicate that the use of a muscle relaxant besides an analgesic or a sedative improves patient safety during intubation. The use of a muscle relaxant can improve intubation conditions but can also be used to prevent or treat chest wall rigidity that is a common side effect of analgesics, mainly fentanyl and remifentanil.

Multiple muscle relaxants are available but there is no clear evidence on which muscle relaxant is most effective and safe in the neonatal population. Succinylcholine was frequently used previously, but has been abandoned because of rare but serious side effects such as malignant hyperthermia and acute rhabdomyolysis with hyperkalemia.[34,46] This has led to the use of the non-depolarizing muscle relaxants atracurium, mivacurium and rocuronium in the neonatal population,[34,44,46,47] but without comparison between different muscle relaxants. Important for a muscle relaxant when used as premedication for endotracheal intubation is a short duration of action, to allow for quick recovery of spontaneous respirations which contribute to tidal volumes and, therefore, lead to lower inspiratory peak pressures during volume targeted ventilation. Mivacurium seems a suitable candidate, with a short onset of effect and a mean duration of action between 11 and 16 minutes in the newborn population.[34,46] There have been availability issues with mivacurium in some countries, for example North America,[32] but this does not apply for the Netherlands. Rocuronium also has a rapid onset of action but has a longer duration of muscle relaxation of up to 1 hour, which is probably to long for this purpose. Feltman et al. could not reproduce this relative long duration of action and found a duration of paralysis of 16 minutes.[44] This could make rocuronium a suitable candidate, but further research is needed. Another important factor is that the muscle relaxant should have a shorter period of action compared to the analgesic/sedative that is used, to prevent patients from being consciously paralyzed.

The majority of studies investigating the combination of a vagolytic, an analgesic and a muscle relaxant, used fentanyl as the analgesic.[34,44-46,50] The choice for fentanyl is based on its fast speed of onset and its cardiovascular stability. There are no clear guidelines as to the dose of fentanyl that should be used to provide sufficient analgesia for this purpose, and the fentanyl dose that was used differed across studies.[34,44,46,50] Data on the pharmacodynamic effects of fentanyl as premedication for endotracheal intubation are not available. It is, therefore, unclear how much fentanyl should be administered to eliminate the pain and discomfort that accompany the act of laryngoscopy. More research into the effects of fentanyl for this purpose is needed, but when administered as part of a premedication strategy also containing a muscle relaxant, this is difficult to examine because paralysis has a clear influence on the behavioral responses to pain. Chest wall rigidity is one of the most frequent and serious complications of fentanyl. In the neonatal population, the risk of chest wall rigidity after fentanyl administration has been estimated at 1.4 to 4%.[51,52] More recent studies did find comparable incidences.[34,45] Chest wall rigidity can be prevented by slow infusion, and can be treated with the use of a muscle relaxant or naloxone,[32] the latter obviously also abolishing the analgesic effect of fentanyl. Dempsey et al. used a strategy in which the muscle relaxant was administered prior to fentanyl to prevent chest wall rigidity, and indeed this side effect did not appear in their study population.[46] The use of a muscle relaxant prior to an analgesic, however, causes the patient to be conscious while being paralyzed and raises ethical questions.

Over the past decade, interest arose into single drug premedication strategies with a short duration of action. Based on its rapid onset of action and very short half-life, remifentanil seemed a suitable candidate in this perspective. Four studies have used different doses of remifentanil as a single drug and found conflicting results both on sedative effect and on the occurrence of side effects. A remifentanil dose of 2 µg/kg was found to cause adequate sedation in all patients in one study, while two studies found doses of 1 µg/kg and 3 µg/kg to cause insufficient sedation in one third of study patients.[50,53,54] In our observational study we found that both with starting doses of 1 µg/kg and 2 µg/kg adequate sedation was very difficult to achieve.[55] Welzing et al. did not observe chest wall rigidity in their patient population and both Avino et al. and Choong et al. found low incidences of 6% and 13% respectively.[50,53,54] We found a much higher incidence of 43%.[55] The dramatic results in our study could be attributed to the fast infusion rate of 30 seconds, causing a shorter duration of effect and higher peak levels with more side effects as a consequence. But even with a more appropriate infusion rate of 60 seconds, the results of several of the abovementioned studies raise concerns about effectivity as well as safety of remifentanil as premedication in the neonatal population. Dose-finding studies are clearly needed to address these issues.

Instead of using remifentanil as a single bolus, it could also be administered as careful continuous infusion with titration up untill sufficient effects are reached, but this strategy also needs further study.

One of the reasons for single drug premedication strategies could be a reduction in preparation times. From this angle, remifentanil might be a less suitable option. Choong et al. described a preparation process including two dilution steps.[50] In our remifentanil study three dilution steps were needed. Although preparation times were not measured, it was time consuming. Besides this, such a complicated preparation process with multiple dilation steps could increase the risk for preparation errors. The predictability of the final concentration in such complicated preparation could also be questioned. We performed a simulated preparation and assessed remifentanil concentrations. In 22% of the tested solutions the actual concentration was below 90% of the intended concentration and in 3% it was above 110%, confirming predictability issues with complicated preparation including several dilutional steps. This issue could be overcome by the use of pharmacy prepared prefilled syringes. The possibility and costs for using remifentanil in this way should be examined.

Another potential single drug candidate is propofol. In 2007, Ghanta et al. published the first randomized controlled trial comparing propofol to the atropine-morphine-suxamethonium combination. Based on the time to successful intubation being more than twice as fast with propofol, the authors concluded that propofol was superior in facilitating endotracheal intubation in neonates. Propofol also had the advantage of maintaining spontaneous respiration, causing less profound hypoxemia and less procedure related trauma.[38] It took more than 10 years for the second report comparing propofol with the opioid-muscle relaxant combination appeared. Durrmeyer et al. showed that there was no difference in the primary outcome of occurrence of prolonged desaturations between atropine-propofol and atropine-sufentanil-atracurium.[56]

Although based on the primary outcomes of these two randomized controlled trials, propofol seemed superior or at least not inferior to the combination of an opioid with a muscle relaxant, some critical remarks should be made. Achieving sufficient sedation appeared much more difficult with propofol. In the study of Durrmeyer et al. additional doses of propofol were needed in over 50% of patients compared to the need for additional atracurium in only about 10% of patients. As a consequence, the use of propofol led to longer procedure times. Also, the quality of sedation based on the intubation conditions was poorer in the propofol group.[55] Ghanta et al. did not specifically report on the need for additional propofol or on the intubating conditions.[38] From a pharmacokinetic perspective, morphine is not a suitable candidate for use as premedication in neonatal

intubation, because of the slow onset of action and slow clearance.[49] The superior effect of propofol compared to the combination of morphine and suxamethonium used by Ghanta et al., therefore, could possibly be influenced by insufficient analgesia and/or sedation by the time intubation was performed. Results could have been different if short-acting opioids had been used.

Several studies provided conflicting results on the sedative effect of different propofol doses.[38,56-58] In all studies equal propofol doses in the entire population of neonates were used, despite the fact that gestational age and postnatal age have been proven to be important determinants of propofol pharmacokinetics.[59] Smits et al. were the first to show that different doses of propofol were needed to provide adequate sedation in groups of neonates with different gestational and postnatal ages.[60] In our NEOPROP-2 trial, a multicenter dose-finding study, we aimed to find the single propofol starting dose that provides effective sedation without side effects in eight groups of patients with different gestational and postnatal ages. Unfortunately, we were not able to establish this propofol dose in any of the eight age groups. We did find that, regardless of gestational age or postnatal age, single propofol starting doses of 1.0 and 1.5 mg/kg almost never led to effective sedation. Only a single dose of 2.0 mg/kg led to effective sedation in the majority of patients. Logistic regression analysis showed that the sedative effect of propofol was not influenced by gestational or postnatal age.[61] From these findings it can be concluded that the sedative effect of propofol is dose-dependent in general, but unpredictable in the individual patient. A meta-analysis of the available studies might provide final conclusions about the appropriate propofol doses.

The existing evidence on the effect of propofol on blood pressure is also conflicting. While in some studies hypotension did not appear[38,62] or did only appear in a small proportion of patients,[56,63] other authors reported a 38 to 65% incidence of hypotension.[57,58,60] The high incidence of hypotension was confirmed in our NEOPROP-2 trial. We found an overall incidence of 59% and incidences of 63%, 52% and 62% in 1.0 mg/kg, 1.5 mg/kg and 2.0 mg/kg starting doses.[61] In a post-hoc analysis of the NEOPROP-2 data we showed that there was a significant decline in blood pressure in all three dosing groups, which was not restored after one hour. This decline in blood pressure was dependent on the starting dose and not on the cumulative propofol dose.[64] In a multiple regression analysis with gestational age, postnatal age, growth restriction (defined as a birth weight below 10th percentile) and male gender as patient variables, we were not able to define factors that could influence the occurrence of propofol-induced hypotension.[61] Other possible influencing factors such as underlying illness and disease severity need further investigation.

Controversy exists regarding the definition of hypotension in neonates as well as the importance of hypotensive episodes in general for the patient. Hypotension in preterm infants has been associated with mortality and serious morbidities.[65-70] Blood pressure, however, is not always the best indicator of circulation and organ perfusion. In this light it has been thought that hypotension in the absence of signs of inadequate tissue perfusion does not yield any long-term negative effects and should not be treated. This phenomenon is referred to as permissive hypotension.[71-73]

To date, there are different opinions as to the importance of propofol-induced hypotension for the neonate. The study of Welzing et al. was terminated prematurely because of the high incidence of hypotension, but the necessity of this termination has been questioned by others.[57,74] Smits et al. found an overall hypotension incidence of 64% but, in the absence of clinical signs of shock, the majority of hypotension episodes were designated as being permissive.[60] Several small studies investigated the relationship between cerebral oxygenation and systemic hypotension after treatment with propofol. An important correlation between blood pressure and cerebral oxygenation was not found in all three studies.[75-77] Although these findings seem to be reassuring, it concerned only small sample sizes and focused on near infrared spectroscopy (NIRS) data only. Clinical short-term and long-term consequences of propofol-induced hypotension have never been investigated. Therefore, the importance of propofol-induced hypotension on the short and long term is yet to be elucidated and might not be as permissive as is thought.

In conclusion, both remifentanil and propofol as single drug premedication strategies possess significant difficulties in providing adequate sedation for the procedure. In addition, both drugs are accompanied by a high risk of side effects. The use of remifentanil as well as propofol as premedication for endotracheal intubation, therefore, should be seriously reconsidered. Based on the current available evidence, in general, the combination of an opioid with a muscle relaxant is the most effective and safe strategy. Fentanyl seems the most suitable opioid candidate. Chest wall rigidity, being a known side effect of fentanyl as well, can be prevented by slower infusion times and can also be overcome by the subsequent use of a muscle relaxant. To prevent patients from being paralyzed while not being sedated, sufficient time should be taken to reach the effect of fentanyl before the muscle relaxant is being administered. Morphine, although one of the drugs most used as premedication,[28-30] should not be used any longer because of its delayed onset and prolonged duration of action. Remifentanil as a single bolus also does not seem a suitable candidate in combination with a muscle relaxant, because its ultrashort period of action that is shorter than that of most muscle relaxants brings the risk of leaving patients paralyzed while the sedative effect has already ceased. Continuous infusion of remifentanil could be considered in combination with a muscle relaxant, but this strategy needs further investigation first.

Rather than focusing on a single premedication strategy that is used within the entire neonatal population, the course should be changed towards a more personalized approach. In the choice for the most suitable premedication strategy, factors such as gestational age and postnatal age, underlying illness, reason for intubation, hemodynamic stability and expected duration of mechanical ventilation should all be considered. In a patient that is being intubated for the purpose of mechanical ventilation for at least several hours, the use of premedication with a very short period of action is probably less important. In these patients, a combination of fentanyl and a short-acting muscle relaxant seems the most appropriate strategy. Propofol should not be used in patients with hemodynamic instability, and probably also in patients who are being at risk for developing hemodynamic instability, such as patients with a sepsis or necrotizing enterocolitis. In these patients, fentanyl in combination with a short-acting muscle relaxant is probably a more appropriate choice. Although muscle relaxants can improve intubation conditions and first attempt success rates, and decrease the incidence of hypoxic events, the use of a muscle relaxant should be carefully considered in every individual patient. Muscle relaxants cause paralysis, also in the respiratory muscles, with subsequent cessation of spontaneous breathing. This is not desirable in every patient or even contraindicated in some categories of patients. This concerns patients with a known or anticipated difficult airway, in whom maintaining a spontaneous breathing pattern is of utmost importance in case of failed intubation and possible difficulty with bag and mask ventilation. Also, in patients with severe respiratory failure, diaphragmatic paralysis due to the use of a muscle relaxant can impair pulmonary function, thereby seriously worsening the course of the disease. In these patients, propofol could be used, provided that the hemodynamic condition is stable. In case of hemodynamic instability in a patient with a known or anticipated difficult airway, both fentanyl and remifentanil as single drug regimens could be considered. However, both should be used with caution with specific attention to the prevention of chest wall rigidity, because this often needs treatment with a muscle relaxant that hampers the respiratory drive.

A significant proportion of drugs in the neonatal intensive care unit is used off label and there are only a limited number of clinical trials on efficacy, dosage and safety of drugs in the neonatal population.[78] This lack of knowledge results in different drug therapies in clinical practice.[79] This certainly applies to the different drugs that are used as premedication for endotracheal intubation in neonates. Information on dosing of these drugs is lacking and doses for the neonatal population are often extrapolated from data in older children and adults. Dose-finding studies in large populations of neonates with clear definitions of effect and side effects are urgently needed to resolve this issue. These studies are, however, difficult to perform. Our NEOPROP-2 trial demonstrates the difficulties that could be encountered when performing such dose-finding trials. Our study had to be

terminated prematurely, one of the reasons for this early termination being the difficulty in including patients in several of the age groups that we defined.[61] Smits et al. encountered the same difficulties in their propofol dose-finding study, with only three out of eight strata containing a sufficiently large sample size.[60] This inclusion difficulty can be explained by the significantly smaller number of neonates with older gestational and postnatal ages that need endotracheal intubation. Awaiting further dose-finding studies, valuable information can be obtained by collecting data on effects and side effects in observational trials. Procedures need to be standardized and effect and side effect registration needs to be part of standard clinical care. To obtain sufficient patient numbers, neonatal centers should pursue collaboration and data-sharing on a national and international level.

READY TO TACK – Towards an individualized premedication strategy

Recommendations for clinical practice

- The choice for a certain premedication strategy should be individualized in every patient, and should be dependent on factors such as gestational and postnatal age, underlying illness, reason for intubation, hemodynamic status and expected duration of mechanical ventilation.
- In general, based on the available evidence, a strategy consisting of a short-acting opioid and a short-acting muscle relaxant seems most effective and safe.
- The use of a muscle relaxant should be carefully considered in every patient. It should not be used in patients with a known or anticipated difficult airway and strongly discouraged in patients with severe respiratory insufficiency.
- Because of difficulties in achieving effective sedation and the significant negative effects on blood pressure, propofol should not be used as a standard premedication regimen. It should only be used in very specific circumstances such as patients with a known or anticipated difficult airway or in whom only a short period of action of the premedication is absolutely required.
- Propofol should not be used in patients with hemodynamic insufficiency and should be carefully considered in patients with a risk of hemodynamic instability.
- When using propofol as premedication, it should be started in a low dose and be titrated according to the sedative effect, under close monitoring of blood pressure.
- Caution is required with the use of remifentanil because of the high risk of chest wall rigidity.

Recommendations for future research

Future research into the most effective and safe premedication strategy for endotracheal intubation should focus on the following aspects:

- Dose-finding of fentanyl and remifentanil as bolus administration.
- The use of remifentanil as a short continuous infusion.
- Comparison of different muscle relaxants.
- Comparison of different premedication strategies in different circumstances.
- National and international collaboration and data-sharing regarding pharmacodynamic and pharmacokinetic data of different strategies.

PREMEDICATION IN LESS INVASIVE SURFACTANT TECHNIQUES

The use of premedication for the INSURE (INtubation – SURfactant – immediate Extubation) procedure has never been questioned. To make immediate extubation after the administration of surfactant possible, the respiratory depression that is often cause by premedication should be very short. Therefore, the premedication strategy should be carefully chosen. A systematic review showed there is not enough evidence on which premedication strategy is most effective and safe in the context of the INSURE procedure.[80] In two smalls studies, remifentanil and propofol as premedication for INSURE were evaluated.[53,57] Both seemed to be effective in providing adequate sedation, but the duration of effect on the respiratory drive was somewhat questionable.[80] In a pilot study on the use of remifentanil for this purpose, we were confronted with serious difficulties in achieving adequate sedation and an unacceptable high incidence of chest wall rigidity, necessitating a premature ending of our study.[55] We had to conclude that remifentanil, at least at a fast infusion rate of 30 seconds, was not suitable for this purpose. In the past years, to the best of our knowledge no new studies have appeared on the use of different premedication strategies prior to INSURE. The question which premedication strategy is best for this purpose, therefore, still remains unanswered. It is, however, undeniable that premedication should be used for the INSURE procedure.

In the past decade, INSURE and also conventional surfactant administration during mechanical ventilation, have increasingly given way to LISA (Less Invasive Surfactant Administration). Comparable to endotracheal intubation and INSURE, LISA requires laryngoscopy, which is known to cause pain and distress. Despite this, LISA procedures

are often performed without premedication to maintain a spontaneous breathing pattern.[81-88] Since LISA failure is associated with a higher need for mechanical ventilation, a higher incidence of supplemental oxygen at day 28 and a 20% lower survival rate without adverse events,[89] maintaining the respiratory drive to prevent LISA from failing is of utmost importance. There is, however, no evidence that laryngoscopy in the context of LISA is not accompanied with pain, discomfort and harmful effects.

In an observational study on LISA without sedative premedication we showed a relatively low first attempt success rate of 52%, a high rate of inadequate technical quality of 41% and a 54% incidence of oxygen desaturations.[90] These results could indicate patient discomfort and intolerance to the procedure and promotes the use of sedative premedication in LISA. In the past three years, several studies have been published evaluating the effect of different kinds of premedication for LISA procedures. Although patient comfort significantly improved,[91,92] both propofol and ketamine did have important negative effects on the respiratory drive.[91-94] Comparing our findings in non-sedated LISA with studies using premedication, showed that our incidence of oxygen desaturations was lower compared to the premedicated population in those studies.[90,92-94] This is most probably due to respiratory depression caused by the premedication. Also, first attempt success rate of LISA was comparable between our study and the studies using premedication.[90,92,94] Premedication did, however, provide better intubating conditions.[90,94] These comparisons do not mean performing LISA in awake patients is acceptable and even better than using premedication. These data do indicate we have to do better in premedicating patients for LISA, using drugs with the least effect on the respiratory drive.

READY TO TACK – Towards premedication use in less invasive surfactant administration

Recommendations for clinical practice

- Laryngoscopy for LISA probably causes equal stress, discomfort and physiological disturbances compared to laryngoscopy for intubation. LISA should, therefore, be performed with premedication.
- The premedication that is used, should have a very short duration of action and should not influence the respiratory drive.
- Results from studies on the use of propofol as premedication for LISA indicate that propofol might have to great an effect on the respiratory drive. Propofol, therefore, seems probably not suitable for this purpose.

Recommendations for future research

- Future research should focus on the most suitable premedication strategy for LISA, that should be very short-acting and without any effect on the respiratory drive.
- Remifentanil is a possible candidate and should be subjected to further research.
- Also, comparative studies of different premedication strategies, preferably in a randomized controlled manner, should be performed to determine the most effective and safe strategy for this purpose.

EXPERIENCE AND COMPETENCE OF THE HEALTH CARE PROVIDER

Endotracheal intubation is a difficult procedure with a relatively low first attempt success rate, even when performed by experienced personnel. However, success of intubation is highly influenced by the degree of experience of the health care provider. Health care providers with variable experience are successful in intubation at the first attempt in 44% to 73% of intubations. Pediatric residents have much lower first attempt success rates that are mainly between 20% and 45%.[3,4,6-9,95,96] In only one study, a success rate of 63% for pediatric residents was found.[5] Pooled data of 8 individual studies showed a first attempt success rate of 42% for pediatric residents, compared to 52% for fellows and 64% for attendings.[11] These data indicate that when being intubated by a pediatric resident the patient is more frequently exposed to multiple intubation attempts. Since an increasing number of attempts increases the risk of adverse events and severe hypoxic events and is also associated with intraventricular hemorrhage and neurodevelopmental impairment, intubation of vulnerable preterm infants by inexperienced airway providers should be prevented.

The opportunities for pediatric residents to acquire and maintain proficiency in neonatal endotracheal intubation is a topic of serious concern. Evidence from anesthesia literature suggests that proficiency at intubation of adults takes over 40 procedures.[97-99] There is no clear evidence as to the amount of procedures needed to become proficient with neonatal intubation. Given the difficulty of the procedure due to the small size of mouth and airway and the anatomy of the larynx in neonates, it is not assumable that the amount of procedures needed to become proficient is lower compared to the adult population.

Due to factors such as an increased presence of advanced practice providers in the NICU and an increased use of non-invasive ventilation strategies, opportunities for pediatric residents to perform neonatal intubation are limited.[1-8,96,100] Nowadays, pediatric residents are graduating without having achieved the competency to intubate a neonate.[7,101] This certainly can be a problem, since pediatricians involved in the care of newborns will be confronted with a neonate requiring endotracheal intubation at some point during their further career. Ways to improve neonatal intubation skills of pediatric residents lay in structured simulation training programs targeting on gaining the skills of neonatal intubation before performing the procedure in real patients.[11] Also, the use of a video laryngoscope, which gives the instructor a view of the upper airway, making it possible to provide clear guidance, has been shown to significantly increase the first attempt success rate of pediatric residents.[102,103]

READY TO TACK – Towards intubation by experienced health care providers

Recommendations for clinical practice

- In each intubation procedure the airway provider should be chosen with careful consideration. Gestational age, weight, the indication for endotracheal intubation and the condition of the patient should be taken into account when deciding who will perform the intubation.
- Urgent and emergency intubations, and intubations in small or unstable patients should be performed by an airway provider skilled in neonatal intubation.
- Efforts to provide adequate intubating experience for pediatric residents should focus on the larger and more stable neonatal population and on simulation training.
- The use of a video laryngoscope can improve the first attempt success rates of inexperienced airway providers and should be considered.

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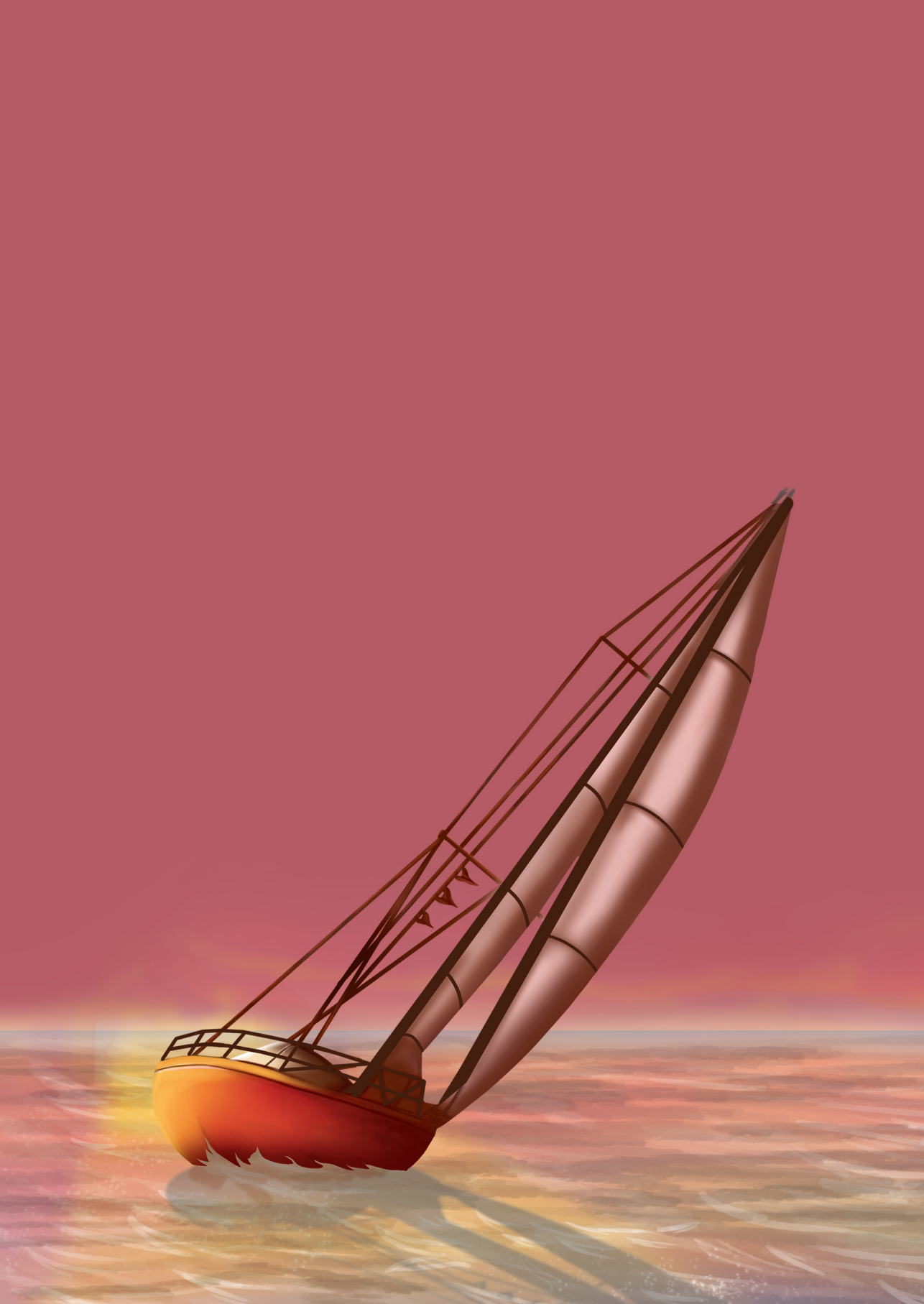
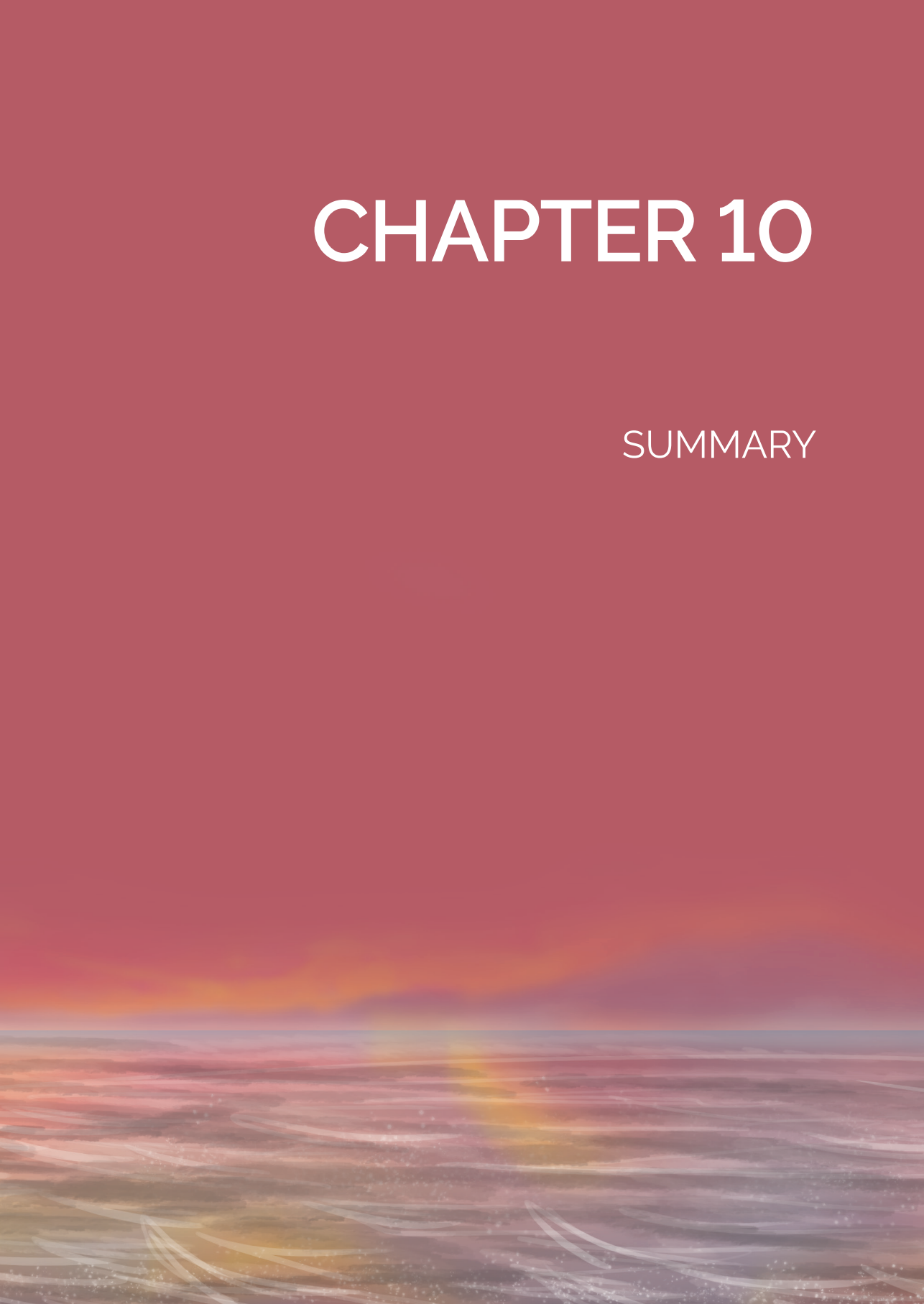


CHAPTER 10

SUMMARY



PREMEDICATION DURING INSURE AND LISA

Respiratory Distress Syndrome (RDS) in preterm infants is often treated with surfactant. Historically, surfactant was administered during a period of mechanical ventilation. To prevent ventilator-induced lung injury, lesser invasive ways to administer surfactant were developed: the INSURE (INtubation-SURfactant-Extubation) procedure and the LISA (Less Invasive Surfactant Application) procedure.

During the INSURE procedure, an endotracheal tube is placed in the trachea and surfactant is administered, followed by immediate extubation. To facilitate immediate extubation, the premedication that is used to provide sedation and comfort during placement of the endotracheal tube, should have a very short period of action, to allow for quick restoration of the respiratory drive.

To determine which drug or combination of drugs would be most appropriate as premedication prior to the INSURE procedure, we performed a systematic review of the literature (**chapter 2**). Our literature search only revealed two publications explicitly evaluating the effect of a certain premedication for the INSURE procedure: remifentanil (2 µg/kg) and propofol (1 mg/kg). Both strategies provided adequate sedation, but the study on propofol was prematurely ended because of serious side effects. In both studies, the time to start with continuous positive airway pressure (CPAP) and the time to extubation were rather long but reasons for this were not provided. The period of action of both remifentanil and propofol could have been too long to enable immediate extubation. An additional search and inclusion of 10 publications describing the use of premedication during INSURE, did not provide enough information about the period of action of different premedication strategies that were used. The results of this review concluded that, although propofol and remifentanil should in theory both be appropriate candidates, further research into the optimal dose, side effects and period of action of both drugs is needed.

Based on its pharmacological profile and the results from our systematic review, we performed a pilot study aiming to evaluate the effect and side effects of remifentanil as premedication prior to INSURE, described in **chapter 3**. Remifentanil was administered as a bolus followed by a saline flush with a total duration of 30 seconds. We started with a remifentanil dose of 1 µg/kg, to be repeated twice in the same dose in case of insufficient sedation. Because this strategy only provided sufficient sedation in one out of five patients, we changed the dosing regimen into a starting dose of 2 µg/kg, with additional doses increasing with 1 µg/kg relative to the previous dose up to a maximum dose of 5 µg/kg in case of insufficient sedation. This regimen led to sufficient sedation

in a higher proportion of patients but also to a high incidence of chest wall rigidity. The study was prematurely ended after the inclusion of 14 patients. The high incidence of chest wall rigidity could have been caused by the fast infusion rate of remifentanil that we used in our study. A fast infusion rate can cause higher peak levels with increased side effects as a consequence. In conclusion, remifentanil as a fast bolus over 30 seconds is not appropriate as premedication for the INSURE procedure.

During LISA, mechanical ventilation is completely avoided and surfactant is administered through a thin catheter that is placed between the vocal cords by laryngoscopy in patients who are spontaneously breathing on nCPAP. Because of the possible depressant effects of premedication on the respiratory drive, LISA is most often performed without the use of premedication, despite the previously gained knowledge on the harmful effects of awake laryngoscopy.

In a prospective observational study described in **chapter 4**, we evaluated the effects of performing a LISA procedure without sedative premedication on the success rate, technical quality of the procedure and vital parameters in preterm newborns. The success rate of the first attempt was 52% and in 41% of procedures the technical quality was inadequate. There was also a strong correlation between success and technical quality. These results could point to patient discomfort and intolerance. Analysis of vital parameters in a subpopulation of study patients in whom vital parameter data were available, showed that heart rate was significantly higher in the first 30 minutes after start of the LISA procedure compared to baseline. Bradycardia <80/min did not occur. These results are most probably attributable to the administration of atropine, which was standard procedure. At 1 and 2 minutes after the start of the LISA procedure oxygen saturation was significantly lower compared to the oxygen saturation before start of the LISA procedure. Besides this, oxygen desaturations <80% in the first 30 minutes occurred in 54% of patients. These desaturations probably do not only reflect an effect of awake laryngoscopy, but also the administration of surfactant. From the results of this study it can be concluded that performing LISA procedures without sedative premedication is accompanied by a low success rate and frequent inadequate technical quality. The use of sedative premedication could improve success and technical quality, and possibly also decrease the incidence of oxygen desaturations to some extent. The use of atropine seems to have a preventive effect on bradycardia and should, therefore, be considered.

MEASUREMENT OF THE EFFECT OF PREMEDICATION

It is well known that laryngoscopy and endotracheal intubation in awake neonates are often associated with adverse physiological events, which can be minimized or prevented by the use of premedication. The purpose of administering premedication, therefore, is to provide a level of sedation sufficient to perform the procedure of intubation without serious adverse events and in the least amount of time. The intubation procedure, therefore, should only be started after this level of sedation is achieved. There is, however, no uniform definition of sufficient sedation and there is much variability in the determination of the level of sedation in clinical practice. In the second part of this thesis we aimed to standardize the intubation procedure by developing an objective scoring system to determine the level of sedation after the administration of premedication.

The first step was to provide insight into the availability of objective and validated scoring systems to assess the level of sedation in the neonatal population. For this purpose, we performed a systematic review of the literature, as described in **chapter 5**. This systematic review showed that there are no validated scoring systems available. A search into studies describing common practice on how level of sedation is determined, revealed 20 studies to be included. In eight of the included studies (40%), the decision to proceed with the intubation after the administration of premedication was not based on the level of sedation. In these studies, intubation was started after a period of time presumed to be enough for drug effect had elapsed, or after the patient was pre-oxygenated. In another eight studies (40%) the decision to proceed with intubation was based on the sedation level, but this was determined subjectively or it was unclear how this was determined. In only four studies (20%) sedation level was evaluated objectively by certain scores. From these studies, a total of three objective sedation assessment tools could be retrieved: the sedation score, based on the motor response after applying a firm stimulus assessed on a 4-point scale; the relaxation score, based on the muscle tone of the extremities also assessed on a 4-point scale; and the sedative state, based on the Neonatal Pain Agitation and Sedation (N-PASS) scale in which 5 items are all assessed on a 5-point scale. The sedation and relaxation scores are both very easy and quickly to perform, the sedative state is a more extensive and time consuming score that is probably less suitable for a situation as acute as neonatal intubation. In conclusion, this systematic review revealed three promising sedation assessment tools, all needing further validation before they can be implemented into clinical practice.

As a second step in this part of the thesis, we developed an Intubation Readiness Score (IRS) that was based on the sedative score that came forward from the systematic review. It consisted of the application of a firm stimulus, rubbing the heel of the patient's foot, and judging the motor reaction to that stimulus on a 4-point scale: 1 = spontaneous

movements; 2 = movement on slight touch; 3 = movement in reaction to the firm stimulus; 4 = no movement. Scores 3 and 4 were believed to indicate a level of sedation that is sufficient to tolerate the act of laryngoscopy and placement of the endotracheal tube. Intubation was only proceeded when a score of 3 or 4 was reached. We implemented this IRS into clinical practice and performed a prospective observational study (**chapter 6**) to evaluate the usefulness of this IRS in predicting the actual level of sedation. For this purpose, the positive predictive value of IRS 3 and 4 in predicting adequate sedation during the intubation procedure was determined. Sedation level was assessed by the intubation score of Viby-Mogensen and adequate sedation was defined as a good intubation score. The results of this study showed a positive predictive value of IRS 3 and 4 of 85%. In 15% of patients there was an inadequate level of sedation based on the intubation score, despite IRS 3 or 4. Univariate analysis revealed no patient factors influencing the ability of IRS 3 and 4 to predict an adequate level of sedation. Based on these results it can be concluded that the IRS is suitable for use in clinical practice but efforts should be made in expanding the score to further improve the positive predictive value. Also, the interrater variability in the firmness of the stimulus and the judgement of the motor reaction should be taken into account.

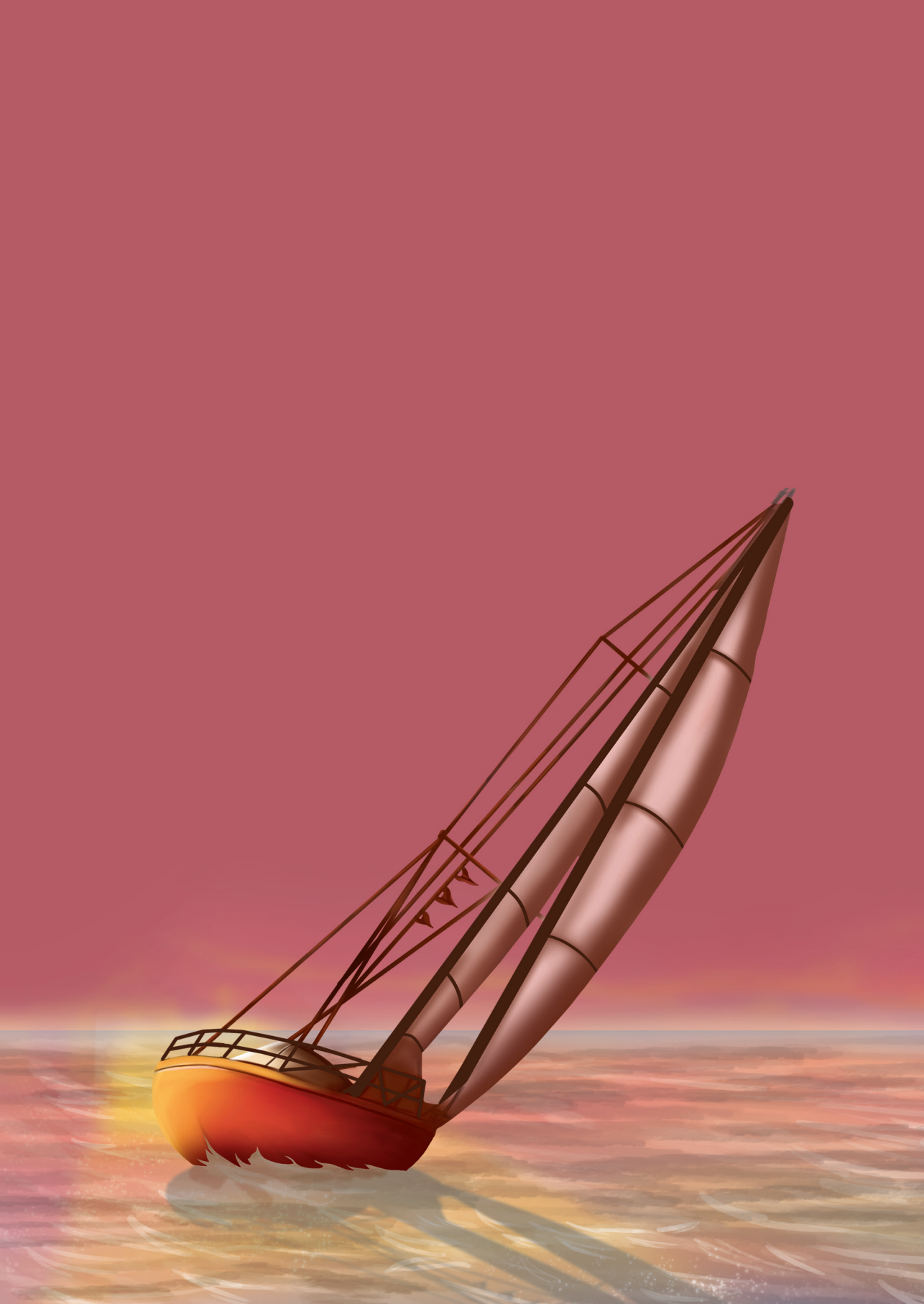
PROPOFOL AS PREMEDICATION

Although the administration of premedication in nonemergency endotracheal intubation is recommended for almost 20 years, there is still no consensus on which premedication strategy is most effective and safe. Propofol is one of the acceptable options and made its way into clinical practice in the last decade. Previously published studies on the use of propofol for endotracheal intubation in the neonatal population showed inconsistencies in the sedative effect of different propofol doses and concerns about its safety.

In the last part of this thesis we aimed to find the optimal single propofol dose providing effective sedation without significant side effects in neonates of different gestational and postnatal ages. We performed a prospective multicenter dose-finding trial, that is described in **chapter 7**. Included patients were stratified into eight different groups based on their gestational age and postnatal age. Dose-finding according to a step-up-step-down model based on sedative effects and side effects was performed in every of the eight groups. After an interim analysis of 91 included patients showed difficulty with inclusion in several of the age groups and a high risk of hypotension, the study was terminated. In two age groups the dose-finding procedure was finished but an optimal single propofol dose providing effective sedation without side effects

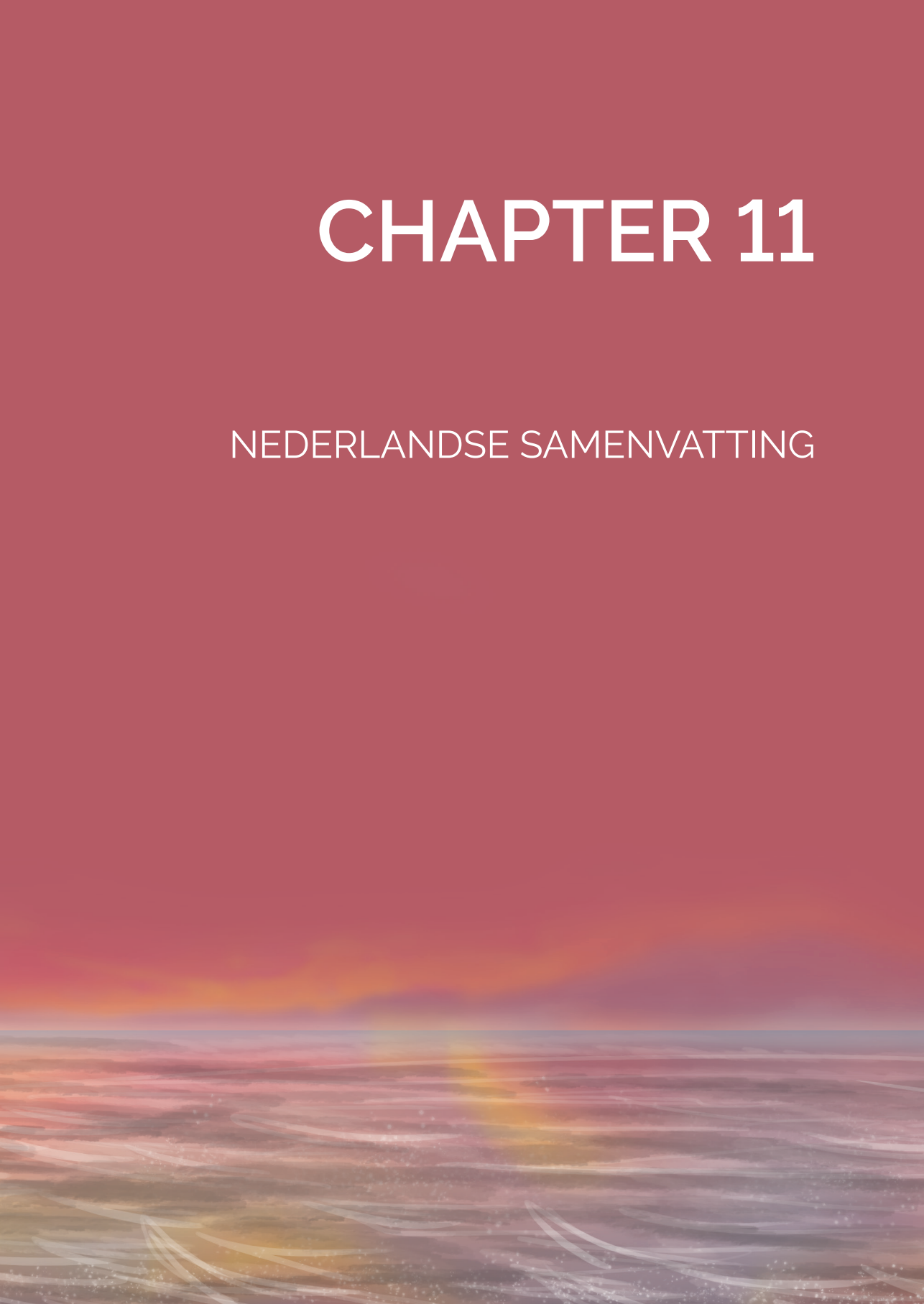
could not be established. In both groups, a propofol dose of 2.0 mg/kg was found to achieve effective sedation, but caused hypotension in more than half of the patients. Further in-depth analysis of the three most used propofol starting doses showed that starting doses of 1.0 and 1.5 mg/kg almost never led to effective sedation. Only a starting dose of 2.0 mg/kg caused effective sedation in the majority of patients. In all three dosing groups, however, more than half of all patients developed hypotension. In the total study population, mean blood pressure after propofol administration decreased with a median of 34% compared to the mean blood pressure at baseline. The lowest mean blood pressure occurred at a median of 21 minutes after the start of propofol administration. Logistic regression analysis showed that gestational age and postnatal age, as well as other patient characteristics, did not influence the sedative effect of propofol and the occurrence of hypotension. Based on these results it can be concluded that effective sedation without the occurrence of side effects is difficult to achieve with a single propofol bolus. Effects as well as side effects of propofol in the neonatal population are variable and unpredictable. Therefore, propofol in the neonatal population should only be used after careful consideration and should be titrated based on sedative effect with strict monitoring of blood pressure.

A post-hoc analysis of the propofol dose-finding trial, aiming to provide guidelines for the use of propofol in clinical practice, studied the effects of different propofol starting doses on blood pressure (**chapter 8**). In both the 1.0 mg/kg, 1.5 mg/kg and 2.0 mg/kg starting doses blood pressure declined after the start of propofol compared to baseline blood pressure before propofol. This decline was dose-dependent, being the largest in the 2.0 mg/kg dosing group. In all three dosing groups, blood pressure was not restored one hour after the start of propofol. The decline in blood pressure was mainly dependent on the starting dose of propofol that was used and not on the cumulative propofol dose that was eventually administered to provide sufficient sedation and accomplish successful intubation. The incidence of hypotension, the treatment of hypotension with volume resuscitation and the maximum decrease in blood pressure as percentage from baseline were all not statistically different between the 1.0 mg/kg, 1.5 mg/kg and 2.0 mg/kg dosing groups. The maximum decrease in blood pressure, however, was significantly earlier in the 1.0 mg/kg dosing group compared to the 2.0 mg/kg dosing group. In conclusion, propofol causes a profound and prolonged decrease in blood pressure that is mainly dependent on the propofol starting dose that is used. These results again stress the need for careful consideration of propofol as premedication in the newborn population. When propofol is used, starting with a low dose and titrating until sufficient sedation is reached, seems to cause the least decline in blood pressure and therefore, seems the safest or least unsafe strategy.



CHAPTER 11

NEDERLANDSE SAMENVATTING



PREMEDICATIE TIJDENS DE INSURE EN LISA PROCEDURES

Pasgeborenen met het Respiratoir Distress Syndroom (RDS) worden vaak behandeld met surfactant. Aanvankelijk werd surfactant toegediend via een endotracheale tube tijdens een periode van positieve druk beademing. Om beschadiging van de longen door positieve druk beademing te voorkomen, werden minder invasieve technieken voor de toediening van surfactant ontwikkeld: de INSURE (INtubation – SURfactant - Extubation) procedure en de LISA (Less Invasive Surfactant Application) procedure. Het eerste gedeelte van dit proefschrift beschrijft onderzoek dat is gericht op het gebruik van premedicatie voor deze procedures.

Tijdens de INSURE procedure wordt een endotracheale tube geplaatst in de trachea, surfactant wordt toegediend en onmiddellijk gevolgd door extubatie. Om deze onmiddellijke extubatie mogelijk te maken, dient de premedicatie die wordt gebruikt ter sedatie en comfort bij het plaatsen van de endotracheale tube een korte werkingsduur te hebben, zodat herstel van de eigen ademhaling snel optreedt.

Om te bepalen welk middel of combinatie van middelen het meest geschikt is als premedicatie voor de INSURE procedure, voerden we een systematische review van de literatuur uit (**hoofdstuk 2**). Uit de zoekstrategie kwamen slechts twee publicaties naar voren die expliciet de effecten van premedicatie voorafgaand aan de INSURE procedure evalueerden: remifentanil (2 µg/kg) en propofol (1 mg/kg). Met beide medicijnen werd adequate sedatie verkregen, maar de studie naar het gebruik van propofol werd voortijdig beëindigd vanwege ernstige bijwerkingen. In beide studies duurde het relatief lang voordat werd overgegaan naar continuous positive airway pressure (CPAP) en extubatie. Redenen hiervoor werden niet beschreven. Dit zou gebaseerd kunnen zijn op een te lange werkingsduur van zowel remifentanil als propofol om onmiddellijke extubatie mogelijk te maken. Een aanvullende zoekstrategie naar studies die het gebruik van premedicatie tijdens de INSURE procedure hebben beschreven, leidde tot de inclusie van 10 studies. Geen van deze studies verschafte voldoende informatie over de werkingsduur van de verschillende premedicatie strategieën die werden gebruikt. Uit de resultaten van deze systematische review kon worden geconcludeerd dat propofol en remifentanil in theorie beiden geschikte kandidaten zouden kunnen zijn als premedicatie voor de INSURE procedure. Verder onderzoek is echter nodig naar de optimale dosering, bijwerkingen en werkingsduur van zowel propofol als remifentanil.

Gebaseerd op de farmacologische eigenschappen en de resultaten van de bovengenoemde systematische review, startten we in de klinische praktijk met het gebruik van remifentanil als premedicatie voor de INSURE procedure. In een prospectieve observationele studie evalueerden we de effecten en bijwerkingen van remifentanil. Deze studie wordt beschreven in **hoofdstuk 3**. Remifentanil werd toegediend als bolus gevolgd door een flush fysiologisch zout met een totale duur van 30 seconden. We startten met een dosering remifentanil van 1 µg/kg. Wanneer onvoldoende sedatie werd bereikt, kon deze dosering tweemaal worden herhaald. Deze strategie leidde slechts bij één van de vijf patiënten tot voldoende sedatie. We veranderden daarom de strategie naar een startdosering van 2 µg/kg. Wanneer sprake was van onvoldoende sedatie, werden extra giften remifentanil toegediend waarbij de dosering steeds werd verhoogd met 1 µg/kg ten opzichte van de voorgaande gift, tot een maximale dosering van 5 µg/kg per gift. Met deze strategie werd bij een groter aantal patiënten voldoende sedatie bereikt, maar het leidde ook tot een hoge incidentie van thorax rigiditeit, een kortdurende maar zeer ernstige bijwerking. Daarop werd na behandeling van 14 patiënten met remifentanil, besloten remifentanil niet meer te gebruiken voor INSURE procedures en werd de studie beëindigd. De hoge incidentie van thorax rigiditeit zou veroorzaakt kunnen zijn door de snelle toediening van remifentanil. Dit zou geleid kunnen hebben tot hogere piek concentraties met een toename van bijwerkingen tot gevolg. Concluderend kan worden gesteld dat remifentanil als bolus in 30 seconden niet geschikt is als premedicatie in het kader van de INSURE procedure.

Tijdens de LISA procedure worden patiënten niet meer invasief beademd, maar wordt surfactant toegediend door een dunne katheter die met behulp van een laryngoscoop tussen de stembanden wordt geplaatst bij patiënten die spontaan ademen met nasale CPAP-ondersteuning. Omdat premedicatie een depressie van de ademdrive kan veroorzaken, wordt LISA meestal uitgevoerd zonder het gebruik van premedicatie, ondanks de kennis over de schadelijke effecten van het verrichten van laryngoscopie in wakkere patiënten.

In een prospectieve observationele studie (**hoofdstuk 4**), evalueerden we de effecten van het verrichten van een LISA procedure zonder het gebruik van sedatieve premedicatie op het succespercentage, de technische kwaliteit van de procedure en de vitale parameters in prematuur geboren neonaten. De eerste LISA poging was succesvol in 52% van de procedures en in 41% van de procedures was sprake van onvoldoende technische kwaliteit. Daarnaast werd een sterke correlatie gevonden tussen succes en technische kwaliteit. Deze resultaten zouden kunnen wijzen op discomfort en verzet van de patiënt. In een subpopulatie van patiënten van wie de vitale parameters beschikbaar waren, werden de hartfrequentie en zuurstofsaturatie geanalyseerd. In de

eerste 30 minuten na de start van de LISA procedure was de hartfrequentie significant verhoogd ten opzichte van de basis hartfrequentie. Bradycardieën <80/min kwamen niet voor. Deze resultaten kunnen waarschijnlijk het beste worden toegeschreven aan het gebruik van atropine voorafgaand aan LISA, wat standaard was in deze studie. Op 1 en 2 minuten na de start van de LISA procedure was de zuurstofsaturatie significant lager dan de basis zuurstofsaturatie voorafgaand aan de LISA procedure. Daarnaast traden bij 54% van de patiënten desaturaties <80% op in de eerste 30 minuten na de start van de LISA procedure. Deze desaturaties zijn waarschijnlijk niet alleen gebaseerd op een effect van de laryngoscopie maar ook op de toediening van surfactant. Uit de resultaten van deze studie kan worden geconcludeerd dat een LISA procedure zonder sedatieve premedicatie leidt tot een laag succespercentage en vaak gepaard gaat met inadequate technische kwaliteit. Het gebruik van sedatieve premedicatie zou het succes en technische kwaliteit kunnen verbeteren. Mogelijk kan ook de incidentie van desaturaties hierdoor worden verlaagd. Het gebruik van atropine lijkt een beschermend effect te hebben op het optreden van bradycardieën en zou daarom overwogen moeten worden.

BEPALEN VAN HET EFFECT VAN PREMEDICATIE

Sinds langere tijd is bekend dat het uitvoeren van laryngoscopie en endotracheale intubatie in wakkere neonaten vaak gepaard gaat met nadelige fysiologische gebeurtenissen. Deze kunnen verminderd of voorkomen worden door het gebruik van premedicatie. Het doel van het toedienen van premedicatie is dan ook een niveau van sedatie te verkrijgen dat voldoende is om de intubatie procedure uit te kunnen voeren zonder ernstige nadelige effecten en in een zo kort mogelijke duur. De intubatie procedure zou dan ook slechts gestart mogen worden wanneer dit niveau van sedatie is bereikt. Er is echter geen uniforme definitie van voldoende sedatie en er is veel variabiliteit in het bepalen van het sedatie niveau in de klinische praktijk. Het tweede deel van dit proefschrift had tot doel om de intubatieprocedure te standaardiseren door het ontwikkelen van een objectief scoresysteem waarmee het niveau van sedatie na de toediening van premedicatie bepaald kan worden.

Allereerst werd inzicht verkregen in de beschikbaarheid van objectieve gevalideerde scoresystemen om het niveau van sedatie te bepalen in de neonatale populatie, door het uitvoeren van een systematische review van de literatuur (**hoofdstuk 5**). Uit deze systematische review kwam naar voren dat er geen gevalideerde scoresystemen beschikbaar zijn. Er volgde een aanvullende zoekstrategie naar studies die beschreven hoe het niveau van sedatie in de praktijk werd bepaald. Dit

leidde tot inclusie van 20 studies. In acht van deze studies (40%) was de beslissing om over te gaan tot intubatie na de toediening van premedicatie niet gebaseerd op het bereikte niveau van sedatie. Intubatie werd gestart nadat een bepaalde tijd was verstreken waarin het effect van de premedicatie werd verondersteld op te treden, of nadat de patiënten gepreoxygeneerd waren. In eveneens acht studies (40%) was het besluit om verder te gaan met de intubatie wel gebaseerd op het niveau van sedatie, maar werd dit niveau subjectief beoordeeld of was onduidelijk hoe dit werd beoordeeld. In slechts vier van de geïncludeerde studies (20%) werd het sedatie niveau objectief beoordeeld, gebruikmakend van verschillende scores. In totaal konden uit deze studies drie objectieve instrumenten ter beoordeling van het sedatie niveau verkregen worden: de sedatie score, gebaseerd op de beoordeling van de motorische reactie na het toedienen van een stevige stimulus op een 4-punts schaal; de relaxatie score, gebaseerd op de beoordeling van de spiertonus van de extremiteiten op een 4-punts schaal; en de sedatieve status, gebaseerd op de Neonatale Pijn Agitatie en Sedatie Schaal (N-PASS) waarbij in totaal 5 items allen op een 5-punts schaal worden beoordeeld. De sedatie en relaxatie scores zijn beiden zeer gemakkelijk in gebruik en snel uit te voeren. De sedatieve status is uitgebreider en tijdrovender en daardoor mogelijk minder bruikbaar voor een acute situatie zoals intubatie bij neonaten. Concluderend zijn er drie veelbelovende instrumenten voor het beoordelen van het niveau van sedatie beschikbaar, welke allen gevalideerd dienen te worden voordat ze kunnen worden gebruikt in de klinische praktijk.

Als tweede stap werd een zogenaamde Intubation Readiness Score (IRS) ontwikkeld om het niveau van sedatie te bepalen. Deze score is gebaseerd op de sedatieve score die naar voren kwam in de systematische review. De IRS bestaat uit de toediening van een stevige stimulus, het krachtig wrijven over de hiel, en het beoordelen van de motorische reactie op deze stimulus op een 4-punts schaal: 1 = spontane bewegingen; 2 = bewegingen op lichte aanraking; 3 = bewegingen in reactie op de stevige stimulus; 4 = geen bewegingen. Bij scores 3 en 4 wordt verondersteld sprake te zijn van voldoende sedatie om de laryngoscopie en het plaatsen van de endotracheale tube te kunnen verdragen. De IRS werd geïmplementeerd in de klinische praktijk en er werd een prospectieve observationele studie verricht (**hoofdstuk 6**) om de geschiktheid van de IRS in het voorspellen van het werkelijke sedatie niveau te evalueren. Hiervoor werd de positief voorspellende waarde van IRS 3 en 4 in het voorspellen van adequate sedatie tijdens de intubatie procedure bepaald. Het niveau van sedatie tijdens de intubatie procedure werd vastgesteld met de intubatie score van Viby-Mogensen. Adequate sedatie werd gedefinieerd als een goede intubatie score. De resultaten van deze studie toonden dat IRS scores 3 en 4 tezamen een positief voorspellende waarde van 85% hadden. In 15% van de patiënten echter, bleek het niveau van sedatie gebaseerd op

de intubatie score inadequaat, ondanks een IRS van 3 of 4. Er werden geen factoren gevonden die invloed hadden op de geschiktheid van IRS 3 en 4 om adequate sedatie te kunnen voorspellen. Gebaseerd op deze resultaten kan worden geconcludeerd dat de IRS een bruikbaar instrument is in de klinische praktijk. Mogelijkheden om de score uit te breiden en daarmee de positief voorspellende waarde te verbeteren moeten worden onderzocht. Eveneens moet meer aandacht besteed worden aan de variabiliteit tussen beoordelaars in het aanbrengen van de stimulus en het beoordelen van de motorische reactie.

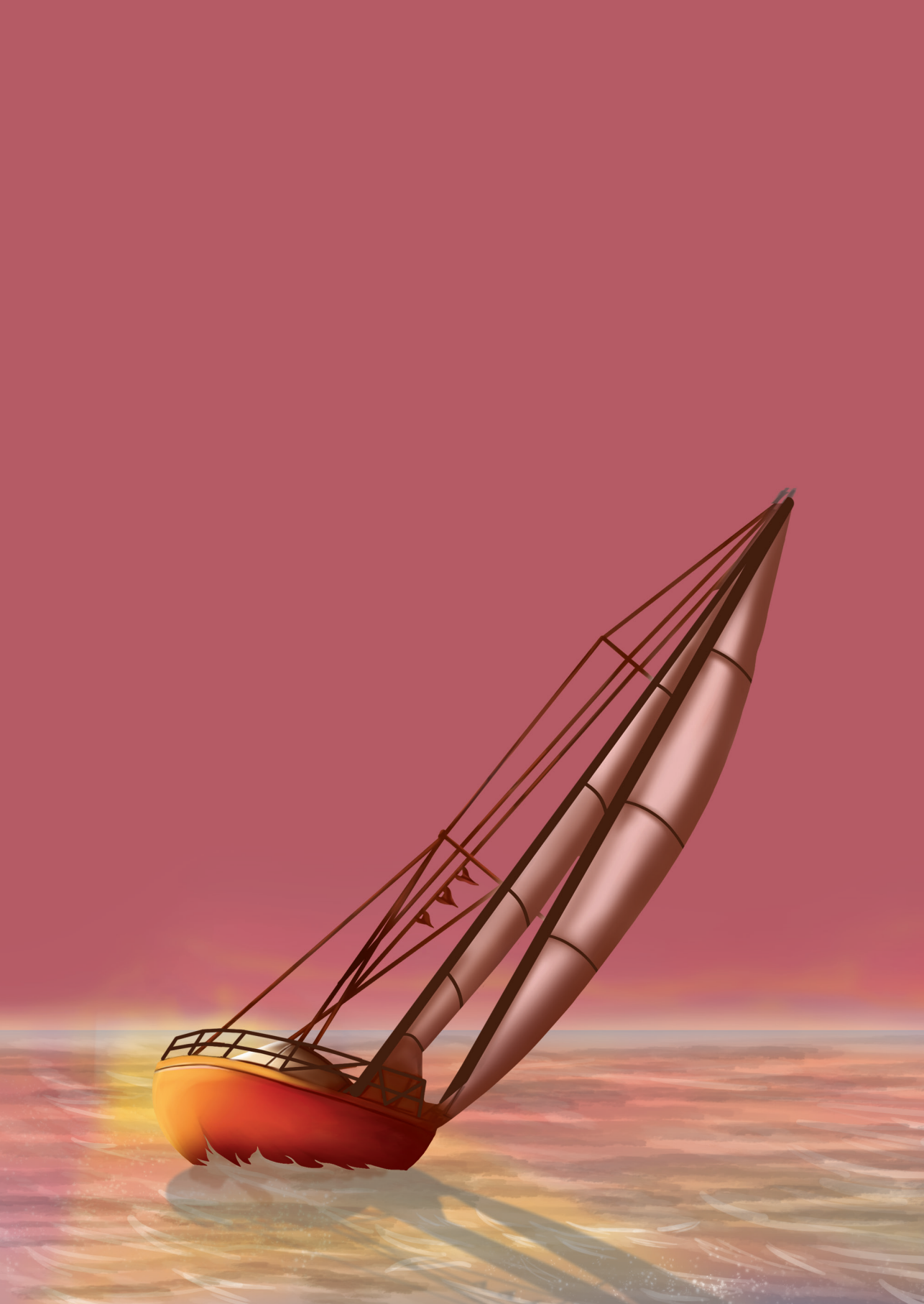
PROPOFOL ALS PREMEDICATIE

Hoewel al 20 jaar geleden werd vastgesteld dat premedicatie altijd gebruikt moet worden voorafgaand aan niet-acute endotracheale intubatie in de neonatale populatie, is de meest effectieve en veilige premedicatie strategie nog altijd niet vastgesteld. Propofol wordt genoemd als een van de mogelijk geschikte opties. In de afgelopen 10 jaar heeft propofol zijn opwacht gemaakt in de klinische praktijk. Eerder gepubliceerde studies naar het gebruik van propofol in de neonatale populatie toonden tegenstrijdigheden in het sedatief effect van verschillende propofol doseringen en tevens zorgen over de veiligheid van propofol gebruik.

Het laatste gedeelte van dit proefschrift is gericht op het vinden van de enkele optimale propofol dosering waarmee effectieve sedatie zonder bijwerkingen wordt verkregen in neonaten. We voerden een prospectieve multicenter dose-finding trial uit, die wordt beschreven in **hoofdstuk 7**. Geïncludeerde patiënten werden onderverdeeld in acht verschillende groepen, gebaseerd op zwangerschapsduur en postnatale leeftijd. In iedere van de acht groepen werd de dose-finding procedure verricht volgens een step-up-step-down model, gebaseerd op de sedatieve effecten en bijwerkingen. Een interim analyse van 91 geïncludeerde patiënten toonde moeilijkheden met de inclusie van patiënten in verschillende leeftijdsgroepen en een hoge incidentie van hypotensie. Om deze reden werd de studie voortijdig beëindigd. In twee van de acht groepen kon de dose-finding procedure volledig doorlopen worden, maar een optimale enkele propofol dosering kon niet worden vastgesteld. In beide groepen bleek dat met een dosering van 2.0 mg/kg voldoende sedatie bereikt kon worden, maar ontwikkelde meer dan de helft van de patiënten hypotensie. Er werd een verdere analyse verricht in de drie meest gebruikte propofol startdoseringen in de gehele studie populatie. Hierbij werd gevonden dat met startdoseringen van 1.0 mg/kg en 1.5 mg/kg bijna nooit voldoende sedatie werd verkregen. Alleen een startdosering van 2.0 mg/kg leidde tot effectieve sedatie bij de meerderheid van de patiënten. In alle drie de groepen ontwikkelde meer dan de

helft van de patiënten hypotensie. Een logistische regressieanalyse toonde dat zowel zwangerschapsduur als postnatale leeftijd niet van invloed waren op het sedatief effect van propofol noch op het optreden van bijwerkingen. Gebaseerd op deze resultaten kan worden geconcludeerd dat het moeilijk is om effectieve sedatie te verkrijgen zonder bijwerkingen met een enkele dosering propofol. De effecten en bijwerkingen van propofol in de neonatale populatie zijn variabel en onvoorspelbaar. Er moet dan ook een voorzichtige afweging gemaakt worden omtrent het gebruik van propofol in de neonatale populatie. Bij gebruik van propofol is strikte monitoring van de bloeddruk noodzakelijk.

Na afronding van de propofol dose-finding trial, voerden we een verdere analyse uit naar de effecten van verschillende propofol startdoseringen op de bloeddruk (**hoofdstuk 8**). In zowel de 1.0 mg/kg, 1.5 mg/kg en 2.0 mg/kg doseringsgroepen daalde de bloeddruk na de start van propofol in vergelijking met de basis bloeddruk voor propofol toediening. Deze daling was afhankelijk van de dosering, en was het meest uitgesproken bij een startdosering van 2.0 mg/kg. In alle drie de groepen was de bloeddruk niet hersteld binnen een uur na de start van de propofol toediening. De daling van de bloeddruk was voornamelijk afhankelijk van de startdosering propofol en niet zozeer van de cumulatieve propofol dosering die uiteindelijk werd toegediend om voldoende sedatie te bereiken en de intubatie te voltooien. Er werden geen verschillen gevonden in de incidentie van hypotensie, de behandeling van hypotensie met volume toediening en de maximale procentuele daling van de bloeddruk tussen de drie doseringsgroepen. Echter, in de 1.0 mg/kg doseringsgroep trad de maximale daling in bloeddruk significant eerder op vergeleken met de 2.0 mg/kg doseringsgroep. Concluderend veroorzaakt propofol een uitgesproken en langdurige daling van de bloeddruk die voornamelijk afhankelijk is van de propofol startdosering die wordt gebruikt. Deze resultaten benadrukken opnieuw dat het gebruik van propofol als premedicatie in de neonatale populatie zorgvuldig moet worden afgewogen. Wanneer propofol wordt gebruikt, dan lijkt het starten met een lage dosering en vervolgens titreren op basis van het sedatief effect de minste invloed op de bloeddruk te hebben en lijkt daarmee de veiligste of minst onveilige strategie.



APPENDICES

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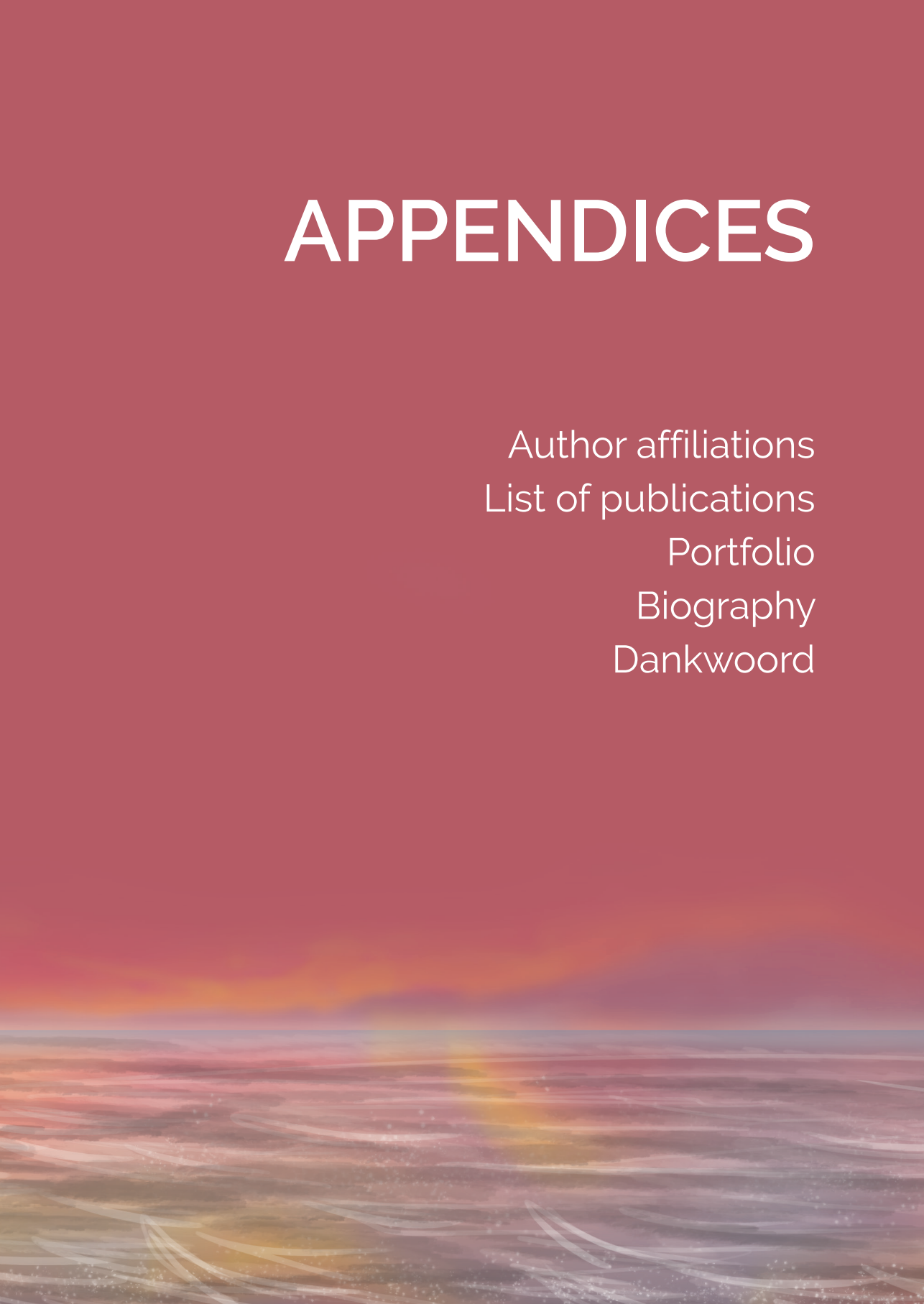

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LIST OF PUBLICATIONS

Publications related to this thesis

De Kort EHM, Twisk JWR, van t Verlaat PG, Reiss IKM, Simons SHP, van Weissenbruch MM. Propofol in neonates causes a profound and protracted decrease in blood pressure. Acta Paediatrica 2020. doi. 10.1111/apa.15282 [Online ahead of print].

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Other publications

Fustolo-Gunnink SF, Fijnvandraat K, Van Klaveren D, Stanworth SJ, Curley A, Onland W, Steyerberg EW, **de Kort E**, d'Haens EJ, Hulzebos CV, Huisman EJ, de Boode WP, Lopriore E, van der Bom JG. Preterm neonates benefit from low prophylactic platelet transfusion thresholds despite varying risk of bleeding or death. Blood 2019;134:2354-2360.

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Dambacher WM, **de Kort EHM**, Blom WM, Houben GF, de Vries E. Double-blind placebo-controlled food challenges in children with alleged cows' milk allergy: prevention of unnecessary elimination diets and determination of eliciting doses. Nutritional Journal 2013;12:12-22.

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PHD PORTFOLIO

Name PhD candidate	Ellen H.M. de Kort
PhD period	January 2016 – December 2019
Promotor	Prof. Dr. I.K.M. Reiss
Copromotors	Dr. S.H.P Simons
	Dr. P. Andriessen
Departments	Division of Neonatology, Department of Pediatrics, Erasmus UMC Sophia Children's Hospital Rotterdam
	Department of Pediatrics, Máxima MC Veldhoven

PHD TRAINING	Year	ECTS
General courses		
• Good clinical practice (GCP) course plus exam	2012	0.6
• GCP certificate renewal	2017	0.3
• Patient oriented research: design, conduct and analysis	2017	0.3
• Biostatistical methods 1: basic principles part A	2019	2.0
• Scientific integrity	2019	0.3
Seminars and workshops		
• Scientific meeting of the neonatology section of the Dutch Association of Pediatrics, 's-Hertogenbosch, the Netherlands	2016	0.3
• Symposium of the Dutch working group on neonatal follow up, Leiden, the Netherlands	2017	0.3
• Basic Clinical Teaching	2017	0.6
• Scientific meeting of the neonatology section of the Dutch Association of Pediatrics, Nieuwegein, the Netherlands	2018	0.3
Oral presentations		
• Prospective evaluation of remifentanil during INSURE in preterm newborns: unpredictable effects and side effects. European Academy of Pediatric Societies, Barcelona, Spain	2014	1.0

• Premedication for neonatal intubation: a search for the most effective and safest strategy. V&VN conference Veldhoven, the Netherlands	2018	1.5
• Propofol for endotracheal intubation in neonates causes a dose-dependent profound and protracted decrease in blood pressure. Joint European Neonatal Societies (jENS), Maastricht, the Netherlands	2019	1.5

Poster presentations

• Are neonates ready to be intubated? Validation of an intubation readiness score. Pediatric Academic Societies, San Francisco, USA	2017	0.75
• Propofol dose finding trial for endotracheal intubation in preterm Newborns. Pediatric Academic Societies, Toronto, Canada	2018	0.75
• Evaluation of success, technical quality and vital parameters in less invasive surfactant administration (LISA) without sedative premedication. Joint European Neonatal Societies (jENS), Maastricht, the Netherlands	2019	0.75
• Success rate of neonatal intubation with two different premedication strategies. Joint European Neonatal Societies (jENS), Maastricht, the Netherlands	2019	0.75

National and international conferences

• Hot Topics in Neonatology, Washington, USA	2016	1.0
• Pediatric Academic Societies conference, San Francisco, USA	2017	1.0
• 2nd International workshop on intensive care of the newborn, Verona, Italy	2018	0.6
• Pediatric Academic Societies conference, Toronto, Canada	2018	1.0
• Joint European Neonatal Societies (JENS) conference, Maastricht, the Netherlands	2019	1.0

Other activities		
• Managing thrombocyte transfusions in a special subgroup: neonates (MATISSE), local principal investigator	2014 - 2018	2.5
• 5 year follow up after hydrocortisone or placebo to prevent bronchopulmonary dysplasia in preterm infants (STOP-BPD), local principal investigator	2017 - present	1.0
• Extremely preterm infants, Dutch analysis on follow up (EPI-DAF), local principal investigator	2017 – present	1.0
• Member of the Dutch working group on neonatal follow up	2016 - present	1.5
• Member of the Dutch working group on neonatal pharmacology	2018 – present	0.3
• Review and implementation of a new electronic patient record and patient data management system (HIX, Chipsoft)	2017 - present	4.0

TEACHING ACTIVITIES	Year	ECTS
Lecturing		
• Organization and development of the local education program for pediatric residents in Máxima Medical Center Veldhoven	2016 - present	2.0
• Participation in the local education program for pediatric residents in Máxima Medical Center Veldhoven on the following topics: • Neonatal life support • Respiratory diseases, diagnostics and treatment • Non-invasive and invasive respiratory support • Neonatal endotracheal intubation • Neonatal follow up • Trombocytopenia	2016 - present	2.5
• Participation in the neonatal intensive care nurse training program on the following topics: • Lung physiology • Respiratory diseases, diagnostics and treatment • Non-invasive respiratory support • Conventional mechanical ventilation • Neonatal follow up • Endocrine and metabolic diseases of the newborn	2016 - 2019	2.0

Coaching		
• Supervisor medium care neonatology and intensive care neonatology internships for residents in pediatrics and development of the internship programs	2016 - present	3.0
• Trainer for fellows in neonatology	2017 - present	2.0
• Coaching of a master student Human & Technology (Zuyd University of Applied Sciences, Heerlen, the Netherlands) in her research and thesis 'the impact of LISA on vital signs in premature infants'.	2017 - 2018	1.0

ABOUT THE AUTHOR

Ellen de Kort was born on September 10th 1979 in Eindhoven, the Netherlands. She received her Atheneum degree at Pius X College Bladel in 1997. After studying Health Sciences at the University of Maastricht for two years, in 1999 she started with her medical training at the Radboud University Nijmegen. She obtained her medical degree in 2005 and started working as a resident in pediatrics at Máxima MC Veldhoven for 14 months, where her interest in Neonatology was first aroused. In October 2006, Ellen started her residency program in Pediatrics, successively at the Jeroen Bosch Hospital in 's-Hertogenbosch and the Radboud University Medical Center in Nijmegen. In March 2011 she graduated as a pediatrician and started with a fellowship in Neonatology at the Neonatal Intensive Care Unit of the Erasmus UMC Sophia Children's Hospital in Rotterdam. In January 2013 she returned to where her professional career had started. She completed the last 7 months of her fellowship in Neonatology in the Máxima MC in Veldhoven and has since then been working there as a neonatologist.

In 2016, Ellen started her PhD trajectory at the Department of Pediatrics of the Máxima MC in Veldhoven and the Erasmus UMC Sophia Children's Hospital in Rotterdam, which resulted in this thesis.

Ellen lives together with her partner Pim in 's-Hertogenbosch. They like to spend their free time on the water in their sailing boat.