Original Article

SAGE Open Medicine

SAGE Open Medicine
Volume 7: 1–4

DOI: 10.1177/2050312119838417
journals.sagepub.com/home/smo
SAGE

The evaluation of the efficacy and safety of non-invasive neurally adjusted ventilatory assist in combination with INtubation-SURfactant-Extubation technique for infants at 28 to 33 weeks of gestation with respiratory distress syndrome

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Abstract

Objectives: The aim of this study is to evaluate the efficacy and safety of non-invasive neurally adjusted ventilatory assist used after INtubation-SURfactant-Extubation in preterm infants with respiratory distress syndrome.

Methods: We conducted a prospective observational study that included 15 inborn preterm infants at 28 (0/7) to 33 (6/7) weeks of gestation with respiratory distress syndrome in the period from April 2017 to October 2018. After INtubation-SURfactant-Extubation, infants underwent non-invasive neurally adjusted ventilatory assist. INtubation-SURfactant-Extubation failure was defined as follows: fraction of inspired oxygen requirement >0.4, respiratory acidosis, and severe apnea within 5 days after surfactant administration.

Results: Two of the 15 (13.3%) infants showed INtubation-SURfactant-Extubation failure and required mechanical ventilation. No infants experienced any major complications such as pneumothorax, patent ductus arteriosus ligation, severe intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, or death.

Conclusion: The rate of INtubation-SURfactant-Extubation failure when non-invasive neurally adjusted ventilatory assist was used after INtubation-SURfactant-Extubation for preterm infants with respiratory distress syndrome was 13.3%. Non-invasive neurally adjusted ventilatory assist can be safely performed without severe complications for preterm infants soon after birth.

Keywords

Preterm infants, respiratory distress syndrome, neurally adjusted ventilatory assist, non-invasive ventilation

Date received: 21 November 2018; accepted: 26 February 2019

Introduction

The INtubation-SURfactant-Extubation (INSURE) technique has been shown to decrease the incidence of subsequent need for mechanical ventilation and chronic lung disease (CLD).[1–8] However, extremely premature infants have a higher risk of subsequent need for intubation and mechanical ventilation, and continuous positive airway pressure (CPAP) failure itself has been associated with higher rates of mortality and CLD.[9] Non-synchronized nasal intermittent positive pressure ventilation (NIPPV) and flow-synchronized nasal intermittent positive pressure ventilation (SNIPPV) have been reported to decrease the rate of INSURE failure compared with nasal continuous positive airway pressure (NCPAP). The reported rates of INSURE failure were 15% to 40% with NCPAP,[1–8,10–13] 11.4% to 17% with NIPPV,[10–12] and 6.1% with flow-SNIPPV.[13] Flow-SNIPPV has been reported to decrease breathing effort because of the effect in improving ventilatory–patient interactions compared with NIPPV.[14] Non-invasive neurally adjusted ventilatory assist (NIV-NAVA), another type of SNIPPV, is also available for infants, and

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NIV-NAVA has been shown to improve patient–ventilator interactions even in infants with large air leak compared with using flow-SNIPPV.[15]

No previous studies appear to have evaluated the efficacy of NIV-NAVA after INSURE. What is the rate of INSURE failure when NIV-NAVA is used after INSURE? Furthermore, can preterm infants safely undergo NIV-NAVA soon after birth? Given these important questions, the aim of this study was to evaluate the efficacy and safety of NIV-NAVA used after INSURE for respiratory distress syndrome (RDS) in infants at 28 (0/7) to 33 (6/7) weeks of gestation.

Methods

We conducted a prospective observational study without a control group between April 2017 and October 2018. Inborn preterm infants at 28 (0/7) to 33 (6/7) weeks of gestation with RDS who were admitted to our neonatal intensive care unit were included. We performed CPAP using a face mask by Jackson Rees circuit for spontaneously breathing infants with respiratory distress, tachypnea, or oxygen requirement. RDS in the study was defined as follows: the presence of respiratory distress, tachypnea, oxygen requirement (fraction of inspired oxygen (FiO_2) >0.3 to maintain SpO_2 $>89\%$), and stable microbubble counts $\leqslant 10$ on gastric aspirate.

Exclusion criteria were as follows: surfactant administration at >2 h after birth, asphyxia (5-min Apgar score <7), presence of amniotic fluid contaminated by meconium, presence of major congenital anomalies, prolonged premature rupture of membranes (>120 h), small for gestational age, or unavailability of a respirator for NIV-NAVA.

Soon after the diagnosis of RDS, we performed transient intubation for surfactant administration. Surfacten® (Mitsubishi-Tokyo Pharma, Osaka, Japan) was administered endotracheally at 120 mg/kg, followed by manual ventilation by Jackson Rees circuit. The infant was then extubated in the presence of good spontaneous breathing and oxygenation. After extubation, the infant was treated with NIV-NAVA for at least 24 h using a SERVO-n neonatal ventilator (Maquet Critical Care AB, Solna, Sweden) via a Miniflow adaptor and nasal prongs or masks (Medin Medical Innovations, Olching, Germany) as appropriate for weight. A special electrode-equipped catheter to detect electrical activity of the diaphragm (Edi) (Edi catheter; Maquet Critical Care AB) was inserted for all infants. Initial settings for NIV-NAVA were as follows: positive end expiratory pressure (PEEP): 6 cmH_2O, neurally adjusted ventilatory assist (NAVA) level: 2.0, and apnea time: 5 s. NAVA level was adjusted to maintain Edi maximum $<15\,\mu V$.

Re-intubation and mechanical ventilation were performed for infants showing INSURE failure, defined as meeting $\geqslant 1$ of the following categories: (1) FiO_2 requirement >0.4 to maintain SpO_2 $>89\%$, (2) respiratory acidosis: pH <7.25 and partial pressure of carbon dioxide (pCO_2) >59 mm Hg, and (3) severe apnea: >6 episodes per 12 h of apnea or >2 episodes per 24 h of apnea requiring bag-and-mask ventilation.

The primary outcome of the study was the requirement for mechanical ventilation within 5 days. Secondary outcomes were duration of nasal ventilation and duration of oxygen therapy. Complications included CLD (oxygen requirement at 36 weeks post-menstrual age), patent ductus arteriosus (PDA) ligation, severe intraventricular hemorrhage (IVH; Grade III or IV), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), mortality, severe abdominal distension, feeding intolerance, and Edi catheter–associated complications such as gastric perforation or gastric bleeding.

This study complied with the standards of the Declaration of Helsinki and the current ethical guidelines, and was approved by the Institutional Ethics Board (protocol number: 1871). Written informed consent was obtained from the legally authorized representatives.

Table 1. Subject characteristics.

	Subjects ($N=15$)	
Gestational age (weeks)	30	(28.4–33.7)
Birthweight (g)	1301	(996–1870)
Male	5	(33.3%)
Antenatal glucocorticoid	1	(6.7%)
Maternal pregnancy disease	5	(33.3%)
Cesarean section delivery	15	(100%)
1-min Apgar score	6	(3–8)
5-min Apgar score	8	(7–9)

Values are expressed as median (range) or number of subjects (percentage).

Results

Within the study period, 27 preterm infants born at 28 (0/7) to 33 (6/7) weeks of gestation with RDS were admitted to our neonatal intensive care unit (NICU). Of these, 12 infants met one of the exclusion criteria (surfactant administration at >2 h after birth, $n=5$ patients; no respirator available for NIV-NAVA, $n=3$; asphyxia, prolonged premature rupture of membranes, chylothorax, small for gestational age, $n=1$ each). The remaining 15 infants were eligible for inclusion in the study.

Clinical characteristics of enrolled infants are presented in Table 1. Table 2 shows the primary and secondary outcomes. Two of the 15 infants (13.3%) failed INSURE and received mechanical ventilation (one patient required mechanical ventilation for 4 days because of respiratory acidosis at 3 h after surfactant administration, and one patient required mechanical ventilation for 18 h because of respiratory acidosis at 4 h after surfactant administration). No infants experienced any major complications such as pneumothorax, PDA ligation,

Table 2. Study outcomes.

	Subjects ($N = 15$)	
Primary outcome		
INSURE failure	2	(13.3%)
Secondary outcomes		
Duration of nasal ventilation (days)	29	(8–55)
Duration of oxygen therapy (days)	1	(0–10)
Complications		
O_2 dependent at 36 weeks' PMA	0	(0%)
Pneumothorax	0	(0%)
PDA ligation	0	(0%)
Postnatal steroids	0	(0%)
NEC	0	(0%)
IVH (Grade III or IV)	0	(0%)
PVL	0	(0%)
ROP	0	(0%)
Death	0	(0%)
Severe abdominal distension	0	(0%)
Feeding intolerance	0	(0%)
Gastric perforation	0	(0%)
Gastric bleeding	0	(0%)

INSURE: INtubation-SURfactant-Extubation; PMA: post-menstrual age; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; ROP: retinopathy of prematurity.
Values are expressed as median (range) or number of subjects (percentage).

severe IVH (Grade III or IV), PVL, ROP, death, severe abdominal distension, feeding intolerance, gastric perforation, or gastric bleeding.

Discussion

In this study, we made two important clinical observations. First, the rate of INSURE failure when NIV-NAVA was used after INSURE for preterm infants at 28 (0/7) to 33 (6/7) weeks of gestation with RDS was 13.3%. Second, NIV-NAVA can be safely used without complications such as pneumothorax, IVH, hypotension, severe abdominal distension, or Edi catheter–associated complications for preterm infants soon after birth.

Regarding the first observation, although the INSURE technique has been shown to decrease the incidence of subsequent mechanical ventilation and CLD, the rate of INSURE failure with NCPAP has been reported as 15% to 40%.[1–8,10–13] Randomized controlled trials showed that non-synchronized NIPPV significantly decreased the incidence of INSURE failure (NIPPV: 11.4%–17% versus NCPAP: 20.9%–40%).[10–12] In addition, flow-SNIPPV has been reported to decrease breathing effort because of the effect in improving ventilator–patient interactions compared with NIPPV.[14] A retrospective cohort study showed that flow-SNIPPV compared with NCPAP significantly decreased the incidence of INSURE failure (flow-SNIPPV: 6.1% versus NCPAP: 35.5%).[13] NIV-NAVA is another mode of SNIPPV available for infants. NIV-NAVA was shown to improve patient–ventilator interactions even in infants with large air leak compared with flow-SNIPPV.[15] In this study, the rate of INSURE failure when NIV-NAVA was used for preterm infants with RDS was 13.3%, lower than that of NCPAP and comparable with that of NIPPV or flow-SNIPPV used after INSURE.

In terms of the second observation, NIV-NAVA is a new ventilator approach, and few reports have described its use among preterm infants.[15–18] The finding that NIV-NAVA can be safely used without complications for preterm infants soon after birth is thus important. Asynchronous breathing in NIPPV may increase pneumothorax and fluctuation of blood pressure and brain blood flow. Good ventilator–patient interactions of NIV-NAVA[15] might be one reason why no severe complications associated with assisted ventilation (such as pneumothorax, IVH, hypotension, or severe abdominal distension) were encountered in this study.

There are some limitations of the study. First, it was the observational design, performed after introduction of both NIV-NAVA and INSURE at the same time. No historical controls were available to provide context on the efficacy of NIV-NAVA alone. Second, it was the small sample size of the study. Therefore, there was no gender balance (30% of infants were male), stratification analysis was impossible, and the range of the gestational age of the population studied was wide. Third, the sample size calculation was not performed. Because there was no report of the efficacy of NIV-NAVA used after INSURE for RDS in preterm infants, the estimated rate of INSURE failure which was necessary for sample size calculation was uncertain. Therefore, we conducted this research as a pilot study for larger analysis in the future to make a rough estimate of the rate of the INSURE failure of NIV-NAVA used after INSURE for RDS in preterm infants.

This study demonstrated that the rate of INSURE failure when NIV-NAVA was used after INSURE technique for preterm infants with RDS was 13.3%, and that NIV-NAVA was performed safely without severe complications for preterm infants soon after birth. Randomized controlled studies comparing NIV-NAVA with NCPAP or NIV-NAVA with flow-SNIPPV are needed to confirm the best respiratory support after INSURE for preterm infants with RDS. Moreover, further studies are needed to confirm the safety and efficacy of NIV-NAVA for extremely premature infants at less than 28 weeks of gestation. LISA (less invasive surfactant administration) is an alternative to INSURE and has been a common implementation in the neonatal units. Recent meta-analysis has shown the superiority of LISA to INSURE.[19] The study for evaluation of the efficacy of the combination of LISA and NIV-NAVA is also warranted.

Declaration of conflict of interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from the Seirei Hamamatsu General Hospital Institutional Review Board (protocol number: 1871).

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from the legally authorized representatives.

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References

1. Verder H, Robertson B, Greisen G, et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish Multicenter Study Group. *N Engl J Med* 1994; 331(16): 1051–1055.
2. Verder H, Albertsen P, Ebbesen F, et al. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. *Pediatrics* 1999; 103(2): E24.
3. Dani C, Bertini G, Pezzati M, et al. Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress syndrome among preterm infants <30 weeks' gestation. *Pediatrics* 2004; 113(6): e560–e563.
4. Escobedo MB, Gunkel JH, Kennedy KA, et al. Early surfactant for neonates with mild to moderate respiratory distress syndrome: a multicenter, randomized trial. *J Pediatr* 2004; 144(6): 804–808.
5. Reininger A, Khalak R, Kendig JW, et al. Surfactant administration by transient intubation in infants 29 to 35 weeks' gestation with respiratory distress syndrome decreases the likelihood of later mechanical ventilation: a randomized controlled trial. *J Perinatol* 2005; 25(11): 703–708.
6. Bohlin K, Gudmundsdottir T, Katz-Salamon M, et al. Implementation of surfactant treatment during continuous positive airway pressure. *J Perinatol* 2007; 27(7): 422–427.
7. Stevens TP, Harrington EW, Blennow M, et al. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev* 2007; 4: CD003063.
8. Rojas MA, Lozano JM, Rojas MX, et al. Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. *Pediatrics* 2009; 123(1): 137–142.
9. Dargaville PA, Gerber A, Johansson S, et al. Incidence and outcome of CPAP failure in preterm infants. *Pediatrics* 2016; 138(1): e20153985.
10. Sai Sunil Kishore M, Dutta S and Kumar P. Early nasal intermittent positive pressure ventilation versus continuous positive airway pressure for respiratory distress syndrome. *Acta Paediatr* 2009; 98(9): 1412–1415.
11. Ramanathan R, Sekar KC, Rasmussen M, et al. Nasal intermittent positive pressure ventilation after surfactant treatment for respiratory distress syndrome in preterm infants <30 weeks' gestation: a randomized, controlled trial. *J Perinatol* 2012; 32(5): 336–343.
12. Shi Y, Tang S, Zhao J, et al. A prospective, randomized, controlled study of NIPPV versus nCPAP in preterm and term infants with respiratory distress syndrome. *Pediatr Pulmonol* 2014; 49(7): 673–678.
13. Gizzi C, Papoff P, Giordano I, et al. Flow-synchronized nasal intermittent positive pressure ventilation for infants <32 weeks' gestation with respiratory distress syndrome. *Crit Care Res Pract* 2012; 2012: 301818.
14. Chang HY, Claure N, D'ugard C, et al. Effects of synchronization during nasal ventilation in clinically stable preterm infants. *Pediatr Res* 2011; 69(1): 84–89.
15. Lee J, Kim HS, Jung YH, et al. Non-invasive neurally adjusted ventilatory assist in preterm infants: a randomised phase II crossover trial. *Arch Dis Child Fetal Neonatal Ed* 2015; 100(6): F507–F513.
16. Stein H, Beck J and Dunn M. Non-invasive ventilation with neurally adjusted ventilatory assist in newborns. *Semin Fetal Neonatal Med* 2016; 21(3): 154–161.
17. Gibu CK, Cheng PY, Ward RJ, et al. Feasibility and physiological effects of noninvasive neurally adjusted ventilatory assist in preterm infants. *Pediatr Res* 2017; 82(4): 650–657.
18. Rodrigo FGM, Marti LU, Henriquez GG, et al. Neural breathing patterns in preterm newborns supported with non-invasive neurally adjusted ventilatory assist. *J Perinatol* 2018; 38(9): 1235–1241.
19. Isayama T, Iwami H, McDonald S, et al. Association of noninvasive ventilation strategies with mortality and bronchopulmonary dysplasia among preterm infants: a systematic review and meta-analysis. *JAMA* 2016; 316(6): 611–624.