Outcomes of noninvasive neurally adjusted ventilatory assist and nasal continuous positive airway pressure in preterm infants: a systematic review and meta-analysis

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ABSTRACT

Introduction: The benefits of neurally adjusted ventilatory assist (NAVA) in preterm infants are unclear. This study aimed to explore if noninvasive NAVA is more beneficial for preterm infants than nasal continuous positive airway pressure (NCPAP).

Study design: Meta-analysis was performed in three clinical trials comprising two randomized controlled trials and one crossover study. We compared NIV-NAVA and NCPAP and reported treatment failure, mortality, and adverse events as the primary outcomes.

Results: Three studies including 173 patients (89 of whom underwent NIV-NAVA) were eligible for this meta-analysis. This review found no difference in treatment failure between NIV-NAVA and NCPAP (RR 1.09, 95% CI 0.65 to 1.84; RD 0.02, 95% CI -0.10-0.14; I^2=33%, P=0.23). Similarly, there was no difference in mortality (RR 1.52, 95% CI 0.51-4.52, heterogeneity not applicable). Compared with NCPAP, NIV-NAVA significantly reduced the use of caffeine (RR 0.85, 95% CI 0.74-0.98, I^2=71%, P=0.03).

Conclusions: Compared with NCPAP, there is insufficient evidence to conclude on the benefits or harm of NIV-NAVA therapy for preterm infants. The findings of this review should be confirmed using methodologically rigorous and adequately powered clinical trials.

Key words: *noninvasive ventilation, premature infant, artificial respiration, interactive ventilatory support, bronchopulmonary dysplasia.*

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Acronyms and abbreviations
BPD, bronchopulmonary dysplasia;
CI, confidence interval;
EAdi, diaphragmatic electrical activity signal;
ICU, intensive care unit;
IMV, invasive mechanical ventilation;
MD, mean difference;
NCPAP, nasal continuous positive airway pressure;
NIV-NAVA, noninvasive neurally adjusted ventilatory assist;
NRDS, neonatal respiratory distress syndrome;
OR, odds ratio;
PEEP, positive end expiratory pressure;
PS, pressure support;
RCTs, randomized controlled trials;
RD, risk, difference;
RR, risk ratio.

INTRODUCTION

Preterm birth is reported to be the leading (and increasing) cause of death among children worldwide, currently resulting in one million deaths each year, with NRDS being the most common cause of premature death.[1-3] In recent years, clinicians have prioritized the early application of noninvasive ventilation, and nasal continuous positive airway pressure (NCPAP) is now one of the most common methods of treating NRDS.[4] However, some studies showed that the incidence of pneumothorax in patients who underwent NCPAP was higher than in those who received noninvasive mechanical ventilation and invasive mechanical ventilation (IMV).[5]

Neurally adjusted ventilatory assist (NAVA) is used to monitor

diaphragmatic electrical activity, perceive actual patient ventilation needs, and provide a certain proportion of ventilation support in real time according to the intensity of the diaphragmatic electrical activity signal (EAdi Theoretically, the triggering of NAVA ventilation and conversion of inhalation and exhalation are directly driven by diaphragmatic electromyography, which maximizes man-machine synchronization.[6] Neonates, especially premature infants, may have immature respiratory centers and the respiratory feedback mechanisms may be affected by respiratory diseases, which can all be disruptive to EAdi.[7]

Few studies have compared the prognosis of noninvasive NAVA (NIV-NAVA) and NCPAP. Nonetheless, a systematic review and meta-analysis focusing on preterm infants has never been performed. We focused our systematic review and meta-analysis on preterm infants requiring NIV-NAVA or NCPAP and on noninvasive ventilation-associated complications.

The purpose of this study was to systematically review NIV-NAVA and NCPAP articles to investigate differences in clinically relevant outcomes among premature infants with different respiratory patterns.

METHODS

We systematically retrieved patient outcome data for preterm infants who had undergone NIV-NAVA or NCPAP from PubMed (1941 to 4 Dec. 2020), Embase (1947 to 4 Dec. 2020), Web of Science (1960 to 4 Dec. 2020), Cochrane Library (Issue 12 of 12, Dec.2020) in the form of reported studies.

We defined preterm infants as infants born with an gestational age of less than 37 weeks, according to the criteria developed by the National Institute of Child Health and Human Development Workshop in 2005.[8]

The following MeSH words and free text were used for retrieval: Neurally Adjusted Ventilatory Assist*[Title/Abstract] OR Proportional Assist Ventilation*[Title/Abstract] OR Interactive Ventilatory Support*[Title/Abstract] OR Ventilatory Support*[Title/Abstract], plus nasal continuous positive airway pressure. Additionally, database-specific limiters for randomized controlled trials (RCTs) and neonates were used. We did not apply language restrictions. We also searched the reference lists of any articles selected for inclusion in this review in order to identify additional relevant articles. We searched conference abstracts for relevant unpublished studies. All searches were evaluated according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Due to the nature of this study, ethical approval was not required.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (a) it was a RCT or crossover trial comparing NIV-NAVA and NCPAP in preterm infants; (b) preterm infants with NRDS were randomized to receive respiratory support with CPAP vs NAVA; and it reported more than one of the following primary outcome parameters: need for oxygen, hospital mortality and adverse events. We did not include studies that were non-clinical studies (experimental and basic studies) and observational or retrospective studies. Study protocols, review articles, abstracts, editorials, and animal studies were also excluded.

Outcomes

Primary outcomes included: treatment failure, hospital mortality and adverse events. Treatment failure defined as the need to escalate support to IMV. Data regarding adverse events included: apnea episodes, pneumothorax, intraventricular hemorrhage (all intraventricular hemorrhage and severe intraventricular hemorrhage), bronchopulmonary dysplasia (BPD) and patent ductus arteriosus.

Secondary outcomes evaluated included the need for surfactant treatment based on clinical evaluation, duration of the NIV treatment, hospital length of stay, intensive care unit (ICU) length of stay, and the need for caffeine treatment.

Study selection and quality assessment

All retrieved records were screened and evaluated by two independent researchers (YX and XK). The titles and abstracts of the trials were scanned to exclude studies that were considered irrelevant, and in cases of controversy, the whole team reached a consensus. Data from the included studies were recorded in a standard form recommended by Cochrane.[9] The quality of RCTs was assessed using the Cochrane risk of bias tool.[9] Each study was assessed for (a) random sequence generation (selection bias); (b) allocation concealment (selection bias); (c) blinding of participants and personnel (performance bias); (d) blinding of related outcomes assessment (detection bias); (e) incomplete outcome data

(attrition bias); (f) selective reporting (reporting bias); and (g) other biases.

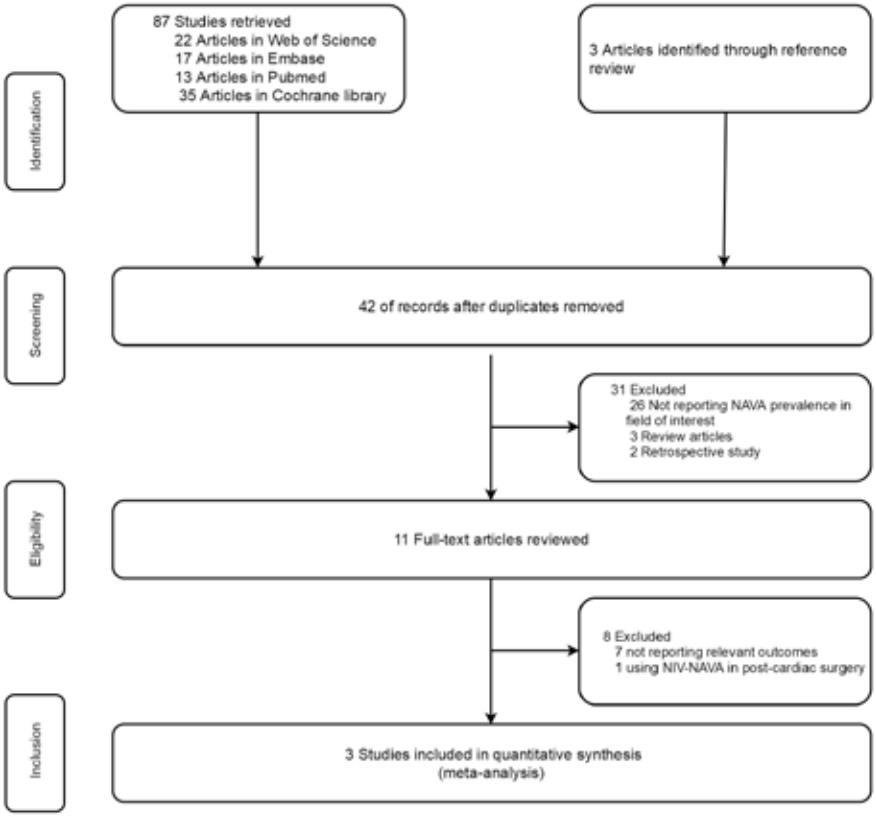
Statistical analysis

Continuous variables were expressed using mean differences (MD) and 95% CI. Categorical variables were expressed using ORs and 95% CIs. A difference test was carried out for the obtained results to determine the heterogeneity between the included studies for each variable. When $I^2<50\%$, there was no obvious difference. Therefore, model analysis resulting in a fixed effect was used. A random-effects model was used if $I^2>50\%$ and Cochran's Q statistic had a P-value ≤0.1. Two independent investigators (JL and XZ) performed the statistical analysis using Cochrane systematic review software Review Manager (RevMan; Version 5.4; The Cochrane Collaboration, 2020). We performed the sensitivity analysis to substitute alternative decisions or ranges of values for decisions that were arbitrary or unclear.

RESULTS

Eighty-seven articles were collected for data extraction, and another three articles were added by manual retrieval of references and reviews. Eighty-seven articles were excluded due to duplication or irrelevancy based on the title or abstract. After the full text of each remaining article was analyzed, a total of three articles were included in the study (*Figure 1*).[10-12] The studies were published in 2019 and representative of a wide distribution of countries. The characteristics of the studies included in the meta-analysis are described in *Table 1*, and patient characteristics are described in *Table 2*. Collectively, these three eligible studies included 173 patients (89 and 84 patients who received NIV-NAVA and NCPAP, respectively). One study[11] was a crossover trial in which patients stayed on a selected mode for a period of time before crossover to an alternate mode, and this study used NIV-NAVA as a weaning technique for preterm infants while other studies used NIV-NAVA before mechanical ventilation.

FIGURE 1. *Flow of studies through database search to inclusion in the meta-analysis*



The database search resulted in 87 articles, and a manual search resulted in an additional three articles. After an initial screening process that excluded duplicate articles, the full text of 11 articles underwent a thorough screening, resulting in three eligible articles.

TABLE 1. *Characteristics of the included studies*

Characteristics		Yagui et al.[10]	Gupta et al.[11]	Kallio et al.[12]
Year of publication		2019	2019	2019
Year of experiment		May 2014 and October 2015, October 2017 and April 2018	July 2014 and June 2015	June 2012 to August 215
Country		Brazil	America	Finland
Age		28-32 weeks	26-34 weeks	32 weeks to 36+6 weeks
Inclusion criteria		Birth weights ≤ 1500 g requiring NCPAP and with a fraction of inspired oxygen ≥25% within the first 48 hours of life	Preterm infants requiring noninvasive ventilatory, support in the neonatal intensive care unit	Postnatal age <48 h and respiratory distress requiring 5-6 cmH_2O CPAP with FiO_2 >0.23 to reach SpO_2 87–93%
Exclusion criteria		Major congenital anomalies; severe perinatal asphyxia (Apgar score at 5 minutes <6); parents refused to consent	Congenital anomalies; grade II or higher interventricular hemorrhage	Weaned to air but required CPAP; invasively ventilated prior to CPAP; chromosomal abnormality; severe congenital anomaly
Purpose		Before ventilation	Before ventilation (first arm); after ventilation (second arm)	Before ventilation
Intervention (NIV-NAVA)	Device	Servo-i ventilator (Maquet, Solna, Sweden)	Servo-i ventilator (Maquet, Solna, Swseden)	Servo-i ventilator (Maquet, Solna, Sweden)
	Setting	The initial PEEP=5 cm H_2O; target PIP=15 ± 5 cmH_2O	The initial NAVA level= 1 cmH_2O/mcV	PEEP=5–6 cmH_2O; NAVA level= 0.1-2.0 $cmH_2O/\mu V$
Control (NCPAP)	Device	Servo-i ventilator (Maquet, Solna, Sweden)	Infant Flow SiPAP system (CareFusion, Yorba Linda, CA)	Infant Flow SiPAP system (Viasys, Healthcare, Pennsylvania, United States)
	Setting	CPAP= 5-7 cmH_2O	CPAP= 3-5 cmH_2O	CPAP= 5–6 cmH_2O

NCPAP, nasal continuous positive airway pressure; NIV-NAVA, noninvasive neurally adjusted ventilatory assist; PEEP, positive end expiratory pressure; PIP, peak inspiratory pressure.

TABLE 2. *Patient baseline data and relevant parameters of assisted ventilation in all included studies (NIV-NAVA/NCPAP)*

Characteristics	Yagui et al.[10]	Gupta et al.[11]	Kallio et al.[12]
Patients, n	59/64	10	20/20
Sex (male %)	22 (40)/34 (57)	5 (50)	10 (50)/13 (65)
Birth weight (mean ± SD, g)	1077.8 ± 259.0/1130 ± 258.4	1265 ± 403	2140 ± 766/2122 ± 766
Gestational age (mean ± SD, weeks)	29.6 ± 2.1/29.8 ± 2.1	29.5 ± 2.9	33.1 ± 2.0/33.0 ± 1.8
Cesarean delivery, n (%)	53 (89)/56(88)	9 (90)	NR
1-min Apgar score, median (IQR)	7 (7-8)/8 (6-8)	6 (5-7)	NR
5-min Apgar score, median (IQR)	9 (8-9)/9 (8-9)	7.5 (7-8)	NR
EAdi peak (mcV)	NR	10.8 ± 3.3/15.6 ± 7.0	NR
EAdi min (mcV)	NR	3.1 ± 0.5/3.2 ± 1.0	NR
HR (rate/min)	NR	150.6/146.9	NR
RR (rate/min)	NR	46.2/49.5	NR
MBP (mmHg)	NR	44.2/43.7	NR
SpO_2 (%)	95.5 (94.0, 98.5)/96.0 (93.5, 97)	97.2/97.1	96.5 (94.0, 98.0)/ 96.0 (93.0, 97.0)
FiO_2 (%)	24.0 (21.0, 31.0)/ 25.0 (21.0, 30.0)	23.8/23.3	26.0 ± 7.0/26.0 ± 4.0

NCPAP, nasal continuous positive airway pressure; NIV-NAVA, noninvasive neurally adjusted ventilatory assist; EAdi, diaphragmatic electrical activity signal; HR, heart rate; RR, respiratory rate; MBP, mean blood pressure; FiO_2, fraction of inspired oxygen; SpO_2, oxygen saturation; SD, standard deviation; IQR, interquartile range.

Criteria on treatment failure

Treatment failure was determined by clinical signs including need for endotracheal intubation, respiratory rate, recurrent apnea, and need for exogenous surfactant. The criteria for treatment failure varied slightly among studies and are summarized in *Table 3*.

Quality and heterogeneity

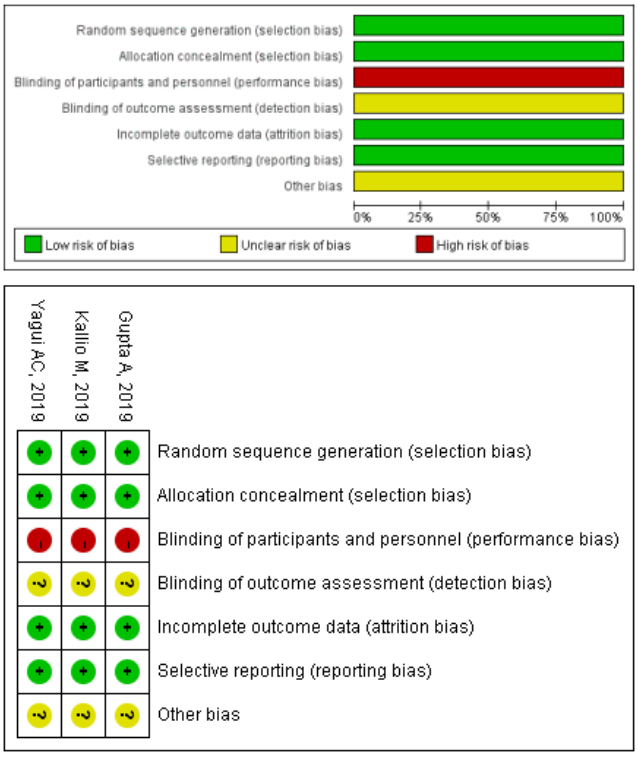
The Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0) was used to evaluate the quality of the RCTs. The bias risks of the included studies are shown in

TABLE 3. *A summary of treatment failure definitions in all included studies*

Characteristics	Yagui et al.[10]	Gupta et al.[11]	Kallio et al.[12]
Oxygenation	$FiO_2 \geq 0.40$ while on CPAP of 7 cmH_2O or NIV-NAVA	Increase in oxygen demand by 10% above the baseline	Increase in FiO_2 to 0.4
Vital signs	NR	Respiratory rate > 80/min, heart rate > 180/min	Excessive work of breathing
Recurrent apnea	Two apnea episodes requiring positive pressure ventilation or >3 apnea episodes/h requiring tactile stimulation	Increase in overall apneic episodes	Frequent apnea
Arterial blood gas	pH < 7.20 and/or PCO_2 > 65 mm Hg for >2 hours	NR	NR
Exogenous surfactant	Second dose	NR	Need for surfactant treatment based on clinical evaluation

NCPAP, nasal continuous positive airway pressure; NIV-NAVA, noninvasive neurally adjusted ventilatory aszsist; FiO_2, fraction of inspired oxygen.

FIGURE 2. *Risk of bias summary*



The quality of the three randomized control trials included in this meta-analysis was assessed using the Cochrane Handbook for Systemic Reviews and Interventions, version 5.1.0. All three studies were found to have a low risk of bias.[18-20]

Figure 2. None of the studies could be blinded for participants, clinicians, or researchers due to the visible and audible differences between the methods of oxygen delivery. However, all studies used objective criteria and measures to assess results that would reduce the risk of ascertainment bias.

Primary outcome

Probability of treatment failure. All studies reported no difference in treatment failure (RR = 1.09, 95% CI = 0.65-1.84; RD = 0.02, 95% CI = -0.10-0.14, I^2 = 33%, P = 0.23; *Figure 3.1*).

Mortality. Overall, mortality of the included studies was low. No significant differences were found in the mortality between NIV-NAVA and NCPAP (RR = 1.52, 95% CI = 0.51-4.52, heterogeneity not applicable; *Figure 3.2*).

Adverse events. No differences were detected between NIV-NAVA and NCPAP in apnea episodes (RR 1.10, 95% CI 0.74 to 1.63, I^2=48%, P=0.17, 2 study involving 163 patients) (*Figure 3.3*). The included studies reported no difference in pneumothorax (RR = 1.38, 95% CI = 0.33-5.83, I^2 = 0, P = 0.61; *Figure 3.4*). In terms of intracranial hemorrhage, BPD, and patent ductus arteriosus, we did not find any significant differences between NIV-NAVA and NCPAP (intracranial hemorrhage: RR = 1.79, 95% CI = 0.77-4.18, I^2 = 0, P = 0.73; bronchopulmonary dysplasia: RR = 0.43, 95% CI = 0.09-2.15, heterogeneity not applicable; patent ductus arteriosus: RR = 0.92, 95% CI = 0.54-1.56, I^2 = 0, P = 0.86; *Figures 3.5-5.7*).

Secondary outcomes

Surfactant therapy. There was no significant difference in surfactant therapy (RR = 0.88, 95% CI = 0.58-1.36, I^2 = 0, P = 0.77). However, there was a trend of higher probability of surfactant therapy in patients with NCPAP compared to in patients with NIV-NAVA (*Figure 3.8*).

Duration of NIV. One study[18] reported no difference in the duration of NIV between patients treated with NCPAP or NIV-NAVA (MD = −20.00, 95% CI = −76.47-36.47; heterogeneity not applicable. One study involved 123 patients) (*Figure 3.9*).

Hospital and ICU stay. We did not find any significant differences between NIV-NAVA and NCPAP[20] with regards to the duration of hospital or ICU stay (ICU stay: MD = -0.30, 95% CI = −6.93-6.33, heterogeneity not applicable, one study involving 40 patients; hospital stay: MD = -2.00, 95% CI = −13.19-9.19, heterogeneity not applicable, one study involving 40 patients; Figures 3.10-3.11).

Use of caffeine. Compared with NCPAP, NIV-NAVA resulted in significantly less frequent caffeine use (RR = 0.85, 95% CI = 0.74-0.98, I^2 = 71%, P = 0.03; *Figure 3.12*).

DISCUSSION

Fifteen million babies are born prematurely every year.[1] Due to immature respiratory tissue and organ development; these infants are at risk for a series of disease states, including NRDS, apnea, and cyanosis. The incidence of NRDS increases with younger gestational age. In a study of 9,575 very premature infants (≤28 weeks' gestation), 93% of subjects were found to have NRDS.[13] According to the Neonatal Research Network, 89% of extremely low birth weight infants have received IMV on their first day of life.[14] The current challenge in the field of respiratory support for premature infants is to provide adequate respiratory muscle load and air exchange with adequate synchronization of respiratory work using appropriate pressure support.[15]

IMV with endotracheal intubation are commonly used. However, IMV complications, including ventilator-associated lung injuries, infection, and bronchopulmonary dysplasia (BPD), can seriously affect the long-term prognosis of premature infants, especially very premature infants.[16-17]

NCPAP increases end-expiratory lung capacity, re-opens collapsed small airways and alveoli, and increases functional residual capacity and lung compliance, thereby improving ventilation and oxygenation, and reducing the intrapulmonary shunt.[18] NAVA uses the electrical activity of the diaphragm to regulate breathing. EAdi represents neural activity and, as an electrical signal, it exists independently of the pressure. Both respiratory support systems provide positive pressure ventilation to prevent alveolar collapse. The unique characteristic of NAVA is that it allows a patient to synchronize spontaneous respiratory effort, and the patient's respiratory drive controls the inspiratory support, which influences an operator-controlled gain

FIGURE 3. *Effective of NIV-NAVA vs NCPAP*

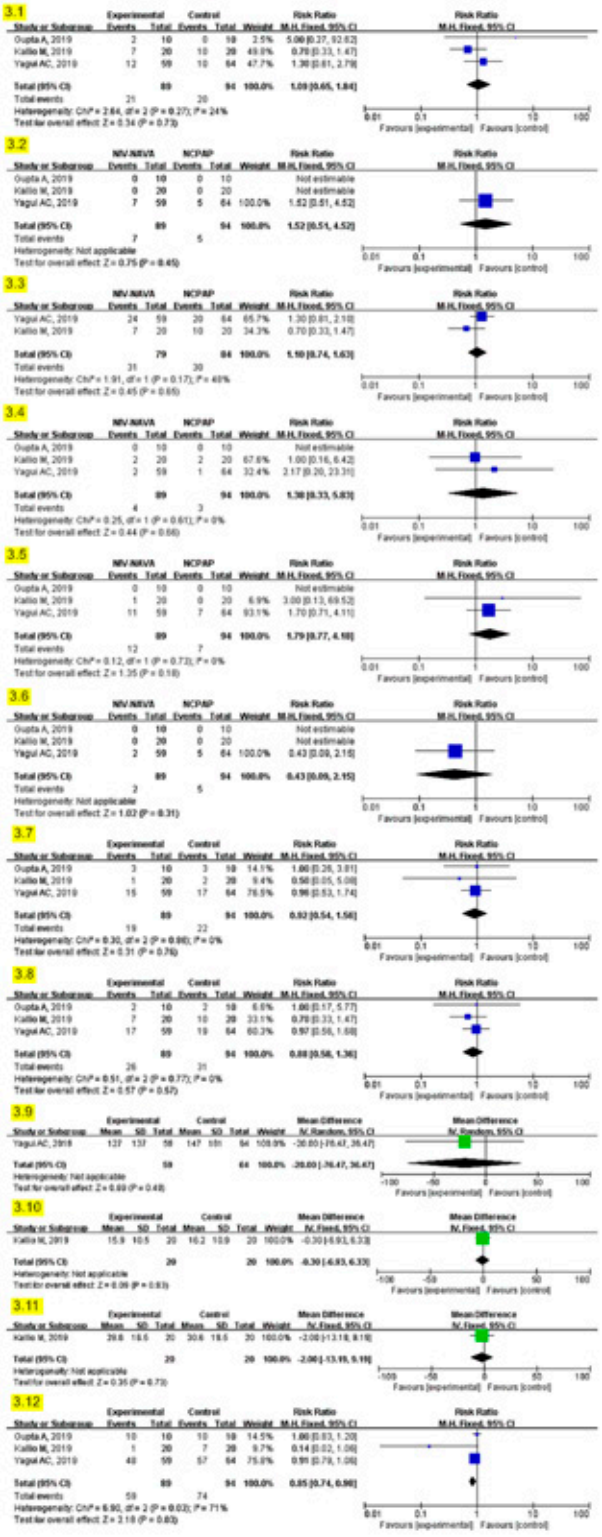


Figure 3.1 treatment failure; Figure 3.2 mortality; Figure 3.3 apnea epidoes; Figure 3.4 pneumothorax; Figure 3.5 intracranial hemorrhage; Figure 3.6 bronchopulmonary dysplasia; Figure 3.7 patent ductus arteriosus; Figure 3.8 surfactant therapy; Figure 3.9 duration of NIV; Figure 3.10 length of ICU stays; Figure 3.11 hospital stays; Figure 3.12 caffeine therapy. NCPAP, nasal continuous positive airway pressure; NIV-NAVA, noninvasive neurally adjusted ventilatory assist; CI, confidence interval.

factor (NAVA level).[19] Theoretically, NAVA is closer to the physiological respiratory mode of respiratory support. Therefore, the use of NAVA can avoid excessive expansion of alveoli, reduce the inflammatory response, and have a pulmonary protective effect. Animal experiments have shown that NAVA is beneficial in triggering switching between inhalation and exhalation. Increased breathing synchronicity can reduce diaphragmatic muscle workload and may play a role in preventing ventilator-related lung and diaphragmatic injuries, reducing circulatory system and distal organ inflammation, and protecting heart and kidney functions.[20-21]

A physiological crossover study exploring the effects of NAVA compared to pressure support ventilation in a pediatric population with moderate acute respiratory distress syndrome presenting difficult weaning from mechanical ventilation found that NAVA significantly reduced the asynchrony index, improved patient-ventilator synchrony, maintaining hemodynamic stability.[22] However, due to the immature development of the nervous system and respiratory center of premature infants, multiple apneas may occur and the incidence is closely related to maturity. Another study suggested that NAVA has no obvious advantage for premature infants and cannot be used as a substitute for NCPAP.[23] In this meta-analysis, we observed no significant difference in treatment failure, death and adverse events between the two groups. This may be due to aggravation of the patient's disease and the need for MV, which is unavoidable. The benefits of NAVA may be limited to patients with severe asynchronous problems and problematic weaning, while the advantages of NAVA are diluted in other populations.[24] However, the studies we analyzed were not performed after MV. During the initiation process of the entire respiratory cycle, NAVA support is directly based on the drive of the patient's respiratory center, and thus determines the actual moisture volume obtained by the patient, avoiding excessive or insufficient ventilation, reducing respiratory muscle exhaustion or insufficient respiratory muscle support, and making weaning difficult. A trial conducted by Beck et al. showed that NAVA is not affected by air leakage and can be effective for patients with non-traumatic air leakage at the junction to reduce respiratory muscle workload and coordinate breathing between the ventilator and patient.[25] A large number of multicenter RCTs have shown that the early use of pulmonary surfactant in children resulted in a lower incidence of pneumothorax, pulmonary stromal emphysema, and BPD and lower mortality rates.[26]

In this meta-analysis, there was no significant difference in the usage rate of pulmonary surfactant between respiratory support groups. However, the dose of pulmonary surfactant was not compared between groups. A recent meta-analysis showed that the prophylactic application of pulmonary surfactant for preterm infants resulted in a higher risk of death or BPD compared with the early application of NCPAP (adding pulmonary surfactant as necessary) (RR = 1.12, 95% CI = 1.02-1.24, P<0.05).[27] As a result, the advantages of prophylactic pulmonary surfactant have not been demonstrated and require further investigation. Compared with NCPAP, NIV-NAVA resulted in significantly lower usage of caffeine. However, the guidelines of caffeine treatment are unclear and have highly subjective influence.

In this meta-analysis, we observed no significant difference in the incidence rates of adverse events (pneumothorax, BPD, patent ductus arteriosus, and intracranial hemorrhage). The optimal positive end-expiratory pressure (PEEP) can be selected according to the EAdi signal; therefore, theoretically, NAVA should have more advantages in organ protection. High PEEP reduces stroke volume, thus reducing cardiac output. However, the articles in this meta-analysis did not include any in-depth discussions about the differences of PEEP. Complications of PEEP such as pulmonary air leakage syndrome, abdominal distension, and nasal injury must be considered.[5] The use of opioids and sedatives also requires further discussion. It must be acknowledged that some of the complications of assisted ventilation currently included are not comprehensive, and further studies are needed for more ventilation parameters (such as PEEP) and long-term prognostic indicators.

We acknowledge that there are some limitations of this study. First, all analyses were based on a small number of studies with

relatively small cohorts/sample sizes. Second, non-randomized studies were included in this meta-analysis, which increased the risk of potential selection and publication biases. Third, treatment within groups was slightly different. Patients in different groups have their own ventilator settings. Lastly, the ventilation settings in this meta-analysis depended on the clinicians' experience and that is not routinely recorded.

CONCLUSION

Due to limited data and very low certainty evidence, we were unable to determine if NIV-NAVA is an effective or safe treatment for preterm infants. Large, adequately powered RCTs are needed to determine whether NAVA is better for premature infants compared to NCPAP, particularly given the potential and long-lasting adverse effects. ■

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