Randomized Crossover Study of Neurally Adjusted Ventilatory Assist in Preterm Infants

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Objective To determine whether neurally adjusted ventilatory assist (NAVA), a new method of mechanical ventilation that delivers pressure assistance that is proportional to the electrical activity of the diaphragm (EAdi), could lower the inspiratory pressure and respiratory muscle load in preterm infants supported with ventilators.

Study design Twenty-six mechanically ventilated preterm infants were randomized to crossover ventilation with NAVA and synchronized intermittent mandatory ventilation (SIMV) with pressure support (PS) for 4 hours each in a randomized order. A 1-hour interval for washout was provided between the 2 modes of ventilation. The ventilator settings were adjusted to maintain similar levels of end-tidal partial pressure of CO_2. The ventilator parameters, vital signs, and gas exchange effects under the 2 ventilatory modes were compared.

Results Nineteen infants completed the 9-hour crossover comparison protocol. Peak inspiratory pressure (PIP), work of breathing, and peak EAdi with NAVA were lower than those in SIMV with PS. Calculated tidal volume to peak EAdi ratio and PIP to peak EAdi ratio were higher with NAVA. There were no significant differences in mean airway pressure, inspiratory oxygen fraction, and blood gas values. The measurements of vital signs did not differ significantly between the 2 modes.

Conclusion NAVA lowered PIP and reduced respiratory muscle load in preterm infants at equivalent inspiratory oxygen fraction and partial pressure of CO_2 of capillary blood in comparison with SIMV with PS. *(J Pediatr 2012;161:808-13)*.

The main objectives of mechanical ventilation in preterm infants include the restoration and maintenance of adequate gas exchange, the reduction of work of breathing (WOB), and the optimization of patient-ventilator interactions, while trying to avoid or minimize ventilator-induced lung injury.[1,2] Though noninvasive respiratory support is the best choice whenever possible to protect fragile premature lungs, mechanical ventilation remains an essential element in the critical care of preterm infants with respiratory distress. Many attempts have been made to develop optimal ventilatory strategies that minimize ventilator-related complications in preterm infants,[3,4] but there is still no consensus as to the best ventilation mode for critically ill preterm newborns.[5,6]

Ideally, assisted mechanical ventilation should provide precisely the amount of support that is needed by the patient. Each breath should not only be supported when initiated by the patient, but this support should also be tailored to the current needs of the patient. One step toward better regulation of assisted mechanical ventilation has been the development of the neurally adjusted ventilatory assist (NAVA) mode.

NAVA is a form of partial respiratory support that is initiated upon the detection of an electrical signal from the diaphragm muscle, and pressure assistance is provided in proportion to and synchronous with the electrical activity of the diaphragm (EAdi).[7] EAdi is recorded by a specially modified naso/orogastric tube that has a sensor that isolates electrical signals of the diaphragm from other electrical signals in the body.[8] The amount of assistance provided for a given EAdi depends on a user-controlled gain factor, called the NAVA level.[9] When phrenic nerves are intact, EAdi is the earliest and best signal available to estimate the neural respiratory drive.[9,10] It is feasible to obtain high-quality EAdi signals in preterm infants, and recent studies indicate that the triggering and cycling-off delays in preterm infants are short enough to safely and effectively control a ventilator.[11,12] Several studies have demonstrated patient–ventilator interaction is improved in NAVA compared with

EAdi	Electrical activity of the diaphragm	PIP	Peak inspiratory pressure
$EAdi_{peak}$	Peak EAdi	PS	Pressure support
$EtCO_2$	End-tidal partial pressure of CO_2	RR	Respiratory rate
FiO_2	Inspiratory oxygen fraction	SIMV	Synchronized intermittent mandatory ventilation
HR	Heart rate	SpO_2	Oxygen saturation
NAVA	Neurally adjusted ventilatory assist	TV	Expiratory tidal volume
PEEP	Positive end-expiratory pressure	WOB	Work of breathing

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other conventional ventilatory modes in children and adults.[13-18] Nevertheless, until recently, few articles have focused on neonates and premature infants.[11,19]

Our goal was to compare the conventional ventilatory mode, synchronized intermittent mandatory ventilation (SIMV) with pressure support (PS), with NAVA to determine whether NAVA could reduce the inspiratory pressure with respiratory unloading. We also asked whether more gentle but safe ventilatory support could be achieved using NAVA in preterm infants.

Methods

A prospective, randomized, controlled, crossover comparison of NAVA and SIMV with PS was conducted from March-August of 2011 in the neonatal intensive care unit of Seoul National University Children's Hospital in Seoul, Korea. Approval for this study was obtained by the Seoul National University Hospital Institutional Review Board, and written informed consent was obtained from the parents of neonates prior to their enrollment in this study. This study was conducted in compliance with the current revision of the Declaration of Helsinki and the Good Clinical Practice guidelines, and registered with ClinicalTrials.gov (NCT01389882).

Preterm infants supported by mechanical ventilation via endotracheal tube who had adequate spontaneous breathing were included in the study. The mandatory mechanical ventilation frequency was below 25 breaths/min. Patients were hemodynamically stable without the use of inotropic agents and were neurologically alert without the use of sedatives or anesthetic drugs. Patients with major congenital anomalies, intraventicular hemorrhage (grade III or higher), or phrenic nerve palsy were excluded from the study.

A pilot study was conducted with 4 preterm infants to test whether NAVA could lower the inspiratory pressure relative to that observed during SIMV with PS. The mean ± SD of the change in peak inspiratory pressure (PIP) was 1.69 ± 2.43 cmH_2O. Based on the pilot results. The required sample size for the main study was calculated to be 10 infants for each group ($\alpha = 0.05$ and $\beta = 0.20$). Therefore, assuming a 20% dropout rate, we estimated that 26 patients would be required for sufficient power to draw conclusions from the study.

Protocol

All of the patients were ventilated using a ventilator with NAVA option (Servo-i; Maquet Critical Care AB, Solna, Sweden). Before beginning the study, the standard orogastric tube was replaced with a specially modified catheter, with an electrode sensor to detect the EAdi (EAdi Catheter; Maquet Critical Care AB). The catheter can also be used for feeding and for venting the stomach. The proper position of the catheter could be identified by the detection of electrical signals by the catheter.

Each infant was studied over 9 hours (Figure 1). SIMV with PS or NAVA was used for 4 hours, and the alternative method of ventilatory assistance was subsequently used for the remaining 5 hours. To rule out carryover effects, a 1-hour washout period was observed after changing the ventilatory modes. The results were only recorded during the 8-hour study period, omitting the 1-hour washout period. The order in which the ventilatory modes were applied was determined by a block randomization method after patient enrollment on the website of the Medical Research Collaborating Center of Seoul National University Hospital. Patients were randomly assigned 1:1 to the 2 groups.

During NAVA, the EAdi was used to control the ventilator. The trigger level was set at 0.5 μV above the minimal

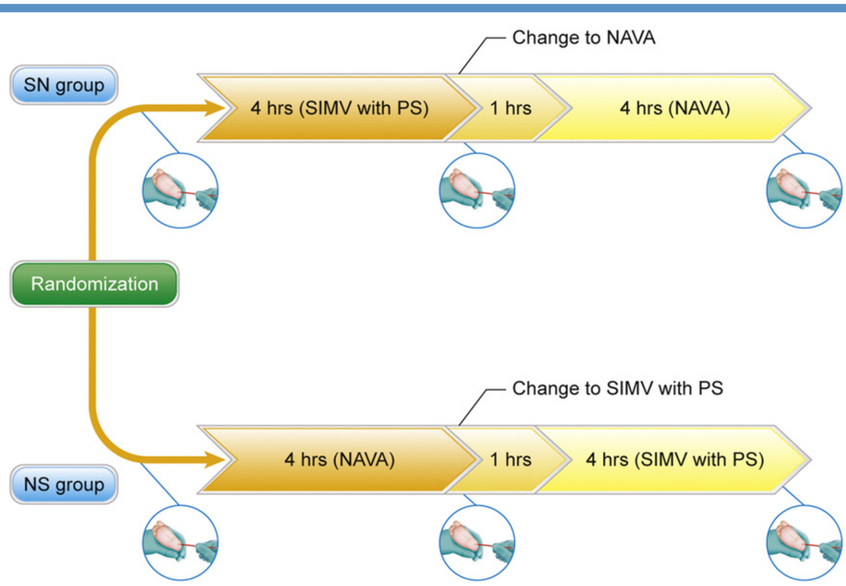

Figure 1. Study protocol.