Mini Review

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The use of neurally-adjusted ventilatory assist (NAVA) for infants with congenital diaphragmatic hernia (CDH)

https://doi.org/10.1515/jpm-2022-0199
Received April 25, 2022; accepted June 8, 2022;
published online July 8, 2022

Abstract

Objectives: Newborns with congenital diaphragmatic hernia (CDH) can have complex respiratory problems which are worsened by ventilatory induced lung injury. Neurally adjusted ventilator assist (NAVA) is a potentially promising ventilation mode for this population, as it can result in improved patient-ventilator interactions and provision of adequate gas exchange at lower airway pressures.

Content: A literature review was undertaken to provide an overview of NAVA and examine its role in the management of infants with CDH.

Summary: NAVA in neonates has been used in CDH infants who were stable on ventilatory support or being weaned from mechanical ventilation and was associated with a reduction in the level of respiratory support.

Outlook: There is, however, limited evidence regarding the efficacy of NAVA in infants with CDH, with only short-term benefits being investigated. A prospective, multicentre study with long term follow-up is required to appropriately assess NAVA in this population.

Keywords: congenital diaphragmatic hernia (CDH); neurally adjusted ventilator assist (NAVA); patient-ventilator synchrony.

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Introduction

Congenital diaphragmatic hernia (CDH) is a developmental defect of the diaphragm resulting in protrusion of abdominal contents into the thoracic cavity [1–3]. It may present as an isolated defect or a component of a syndrome. CDH occurs in between one in 2,500 to one in 3,500 live births in the UK [4]. CDH is associated with a high mortality rate, between 30 and 50% [5] and survivors can suffer chronic respiratory morbidity resulting from pulmonary hypoplasia and pulmonary hypertension.

Lung hypoplasia and atypical remodelling of pulmonary vasculature makes infants with CDH some of the most complex to support with mechanical ventilation (MV) [1–3, 6, 7]. In animal models of CDH, it has also been demonstrated that gas exchange across the alveolar-capillary membrane is diminished [8]. As the management of CDH has moved from early closure to a delayed surgical approach, greater emphasis has been placed on optimising mechanical ventilation (MV) both before and after surgery [9–11]. Mechanical ventilation can cause ventilatory induced lung injury (VILI) and accentuate lung pathology [12, 13]. VILI has been shown to impair postnatal lung development resulting in chronic oxygen dependency (bronchopulmonary dysplasia [BPD]), and chronic respiratory morbidity including abnormalities in lung function and associated respiratory symptoms [14]. Guidelines from the European Congenital Diaphragmatic Hernia (CDH EURO) Consortium recommend routine intubation of neonates with prenatally diagnosed CDH, avoiding high airway pressures and establishing adequate oxygenation and perfusion. Exceptions are neonates with predicted good lung development on pre-natal assessment, who may be offered a trial of spontaneous breathing to avoid VILI [15]. There is limited evidence to determine which ventilatory mode should be used in infants with CDH. In a randomised control trial (VICI-trial) comparing conventional mechanical ventilation (CMV) to high frequency oscillatory ventilation (HFOV), there was no significant difference between the modes with regard to the combined

primary outcome of death and BPD [OR 0.62 (95% CI 0.25–1.55)]. CMV, however, was associated with a reduction in the duration of ventilation [10 (6–18) days] compared to HFOV [13 (8–23 days), p=0.03] [16]. In addition, the CMV group had a reduced requirement for inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO). The CDH Euro Consortium, therefore, recommends CMV as first-line ventilatory support. To reduce VILI, further recommendations include gentle ventilation, aiming for pre-ductal saturations between 80 and 95% and post ductal saturations above 70%. A strategy of permissive hypercapnia is also recommended, aiming for arterial CO_2 levels between 50 and 70 mmHg (6.9 and 9.3 kPa) to avoid further lung damage [15]. Furthermore, peak pressures should be limited to 25 cm H_2O or less and a PEEP of 3–5 cm H_2O used to avoid VILI, however, evidence to support those guidelines are limited [15].

New ventilatory technologies are being introduced into neonatal care and it is important to determine if they may improve outcomes in infants with CDH. One such is neurally adjusted ventilatory assist (NAVA), where ventilatory support is matched to patient demand in response to the electrical activity of the diaphragm (EAdi) [17]. NAVA has been demonstrated to result in short term improvements in very low birth weight infants (VLBW, <1500 g) and those with acute respiratory distress syndrome or BPD [18–20]. In a retrospective study [21], the outcomes of eighteen infants who were supported on NAVA and non-invasive NAVA (NIV NAVA) were compared with 36 historical controls, who were matched by gestational age, birth weight, sex, antenatal steroid exposure and if inborn or transferred ex utero. Infants on NAVA/NIV NAVA had lower extubation failure rates (median 0 (0–2) vs. 1 (0–6) p=0.002), shorter durations of invasive ventilation (median 30.5 (1–90) days vs. 40.5 (11–199) days p=0.046) and total duration of invasive and non-invasive ventilation (median 80 (57–140) days vs. 103.5 (60–246)) days p=0.026. In the CDH population, however, a structurally abnormal diaphragm could reduce the efficacy of NAVA as this ventilatory mode depends on diaphragmatic neural activity. This review aims to provide an overview of NAVA and examine its role in the management of infants with CDH.

Methods

The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) guidelines. A literature search of MEDLINE, Embase and Cochrane Library databases from January 2000 to April 2022 was executed. Key words and MeSH terms pertaining to NAVA and CDH were used to identify articles. Terms included “NAVA”, “neurally adjusted ventilatory assist”, “CDH” and “congenital diaphragmatic hernia”. Reference lists of retrieved literature were also manually searched.

Titles and abstracts were screened and duplicate articles removed. Search strategies were limited to the English language. Editorials, narrative reviews, consensus documents and commentaries were excluded. The quality of eligible studies were assessed using the modified Newcastle-Ottawa scale. No articles were excluded based on their quality.

Data extracted from the included articles were tabulated and then, a narrative synthesis was undertaken to identify key themes in the literature.

Neurally adjusted ventilatory assist

During NAVA, ventilatory support is matched to patient demand in response to the electrical activity of the diaphragm (EAdi) [17]. The EAdi signal is an electromyogram and is the summation of the motor unit action potentials. The EAdi signal is measured using an EAdi catheter (Maquet, Solna, Sweden) which contains nine miniaturised electromyogram detectors positioned at the level of the diaphragm. The electrodes are used to measure Edi peak and Edi minimum (min). Edi peak (5–15 mcV) refers to the amount of electrical activity required to generate each breath, representing neural inspiratory effort. Edi min (0–4 mcV) represents the tonic resting activity between breaths and the electrical activity responsible for maintaining the functional residual capacity (FRC). During NAVA, ventilator inflations are triggered when a threshold change in Edi is reached, usually 0.5 mcV; inflations are delivered earlier in the respiratory cycle compared to when flow triggers are used [18]. The amount that NAVA augments the neonate’s respiratory effort is set by the clinician and is referred to as the ‘NAVA level’. The NAVA level is set according to clinical status of the neonate, those with stiffer (non-compliant) lungs requiring a higher NAVA level.

Both NAVA and proportional assist ventilation (PAV) provide pressure support synchronised throughout the respiratory cycle proportional to the patient’s demand. In a crossover comparison study both NAVA and PAV, compared to baseline conventional ventilation, improved oxygenation, but the mean “A-a” gradient was better on NAVA. That difference may reflect the longer trigger delay with PAV (flow trigger) compared to NAVA [22]. Using triggering from the diaphragm overcomes the challenges of using flow and pressure triggers in neonates who have high respiratory rates and small tidal volumes and may have leaks around their endotracheal tubes which are usually uncuffed [18].

There is, however, a paucity of evidence regarding the efficacy of NAVA from RCTs. Indeed, in the Cochrane review only one RCT was identified and it reported no significant differences in mortality or BPD, but only 60 infants were included [23].

In the CDH population, it was theorised that a structurally abnormal diaphragm could negate the use of a ventilatory method dependent on neural innervation of the diaphragm (NAVA). Yet, despite operative closure of the diaphragm, the EAdi signal can be captured and used to control ventilatory support [24–27]. In a retrospective

case-control study of 16 neonates, the EAdi signal in CDH infants was comparable to that of age and weight-matched controls [25]. Neonates with liver herniation and patch repairs were also still able to transition from invasive ventilation to invasive NAVA [27].

Barriers to the use of NAVA in infants with CDH

The primary barrier to utilising NAVA in CDH is the failure to produce a sufficient EAdi signal. The site and size of the diaphragmatic defect can impact the ability of EAdi to be detected by the electromyogram. Predictably, hemi-diaphragmatic agenesis can lead to signal absence [27, 28]. In one study of 12 neonates with CDH, five with a primary repair had a regular EAdi signal and were successfully weaned with NAVA. Of the seven patients submitted to patch repair, five operated with patch limited to the diaphragmatic posterior-lateral area had an active EAdi signal that permitted weaning with NAVA. Only in two neonates with hemi-diaphragm agenesis was NAVA not possible due to no EAdi signal [28]. Potential further limitations include pleural effusion and chylothorax [26–28]. Although despite fluid accumulating in the ipsilateral hemithorax following surgical repair, EAdi signal was still detected in one series [27]. The EAdi signal may be negatively correlated to the volume of accumulated fluid. Further problems include failure to place the NAVA catheter appropriately, which can be limited by the position of the stomach and the subsequent angle of His [28].

As NAVA relies on the presence of EAdi, treatment with sedating medications which supress the respiratory drive may hinder its effectiveness [27]. Therefore, opioids must be titrated carefully to sufficiently alleviate pain without causing respiratory depression and medically induced apnoea.

Theoretically, the neural trigger is not affected by intrinsic PEEP. Post CDH repair, however. it is common to find the contralateral lung to have compensatory hyperinflation causing the diaphragm to be flat. In that scenario, it has been postulated that the infant may not be able to trigger NAVA, but this has not been recorded as a problem in the case series.

Physiological outcomes of NAVA in CDH infants

Invasive and non-invasive (NIV) NAVA can be used successfully post-operatively in neonates with CDH to wean ventilatory support [24–27]. Several studies investigating post-operative weaning have shown positive inspiratory pressures (PIP) are significantly lower on NAVA than PSV, but with similar minute ventilation, respiratory rate and haemodynamics [24, 25, 29]. In a retrospective cohort analysis of 16 neonates with CDH placed on NAVA over a treatment period of 72 h, there were significant reductions in the PIP and MAP [25]. Lower PIP may reduce the incidence of VILI. In an autopsy study of CDH infants managed with PIPs of greater than30cm H_2O, 91% of specimens had hyaline membrane deposition and diffuse alveolar injury [30]. There are several reasons why PIP may be lower on NAVA. During NAVA, the magnitude of pressure delivered depends on the patient's respiratory drive and the EAdi amplitude. As a result, ventilatory assist is adjusted breath by breath according to patient demand, opposed to a fixed pressure delivered during pressure support ventilation (PSV) [29]. The reduction in PIP seen with NAVA in neonates with CDH, is also likely due to increased patient-ventilator synchrony [17, 24, 25, 29, 31, 32]. Patient-ventilator asynchrony has been shown to result in pneumothorax, interventricular haemorrhage, greater need for sedation and longer duration of ventilation [33–35].

A retrospective case-control study found neonates weaned with NAVA had a lower respiratory severity score (RSS) compared to matched controls [25]. The respiratory severity score (RSS) consists of the fraction of inspired oxygenation (FiO_2) multiplied by the mean airway pressure (RSS = MAP × FiO_2). It has been used as a surrogate for the oxygenation index (OI) to assess the need for respiratory support in infants [36]. Amongst 59 neonates with CDH, raised pre- ($p<0.001$) and post-operative ($p=0.004$) RSS scores were significantly correlated with death.

In a retrospective case-control study, CDH neonates who were being weaned from mechanical ventilation with NAVA had a reduction in their alveolar-arterial oxygen tension difference (A-aDO_2) by a third [24]. A persistently elevated A-aDO_2 has been shown to negatively correlate with survival in neonates with CDH [32].

Clinical outcomes of NAVA in CDH infants

Ten CDH patients on NAVA were weaned and extubated in a shorter time (9.3 ± 3.3 days) than a historically matched group managed with PSV (13.0 ± 4.5 days) [28]. This is an important outcome as review of 60 CDH infants at a single institution, highlighted that a longer duration of MV was correlated with infants developing more long-term complications, including learning difficulties, failure to thrive and intestinal obstruction ($p=0.0016$) [37].

In seven CDH infants, non-invasive (NIV) NAVA was successfully used post extubation in CDH infants. The NIV-NAVA infants were in NICU 50% longer (average 64 days) than their matched counterparts supported by conventional ventilation (average 40 days). That result, however, may have been explained by a greater

proportion of the NIV-NAVA infants requiring pre-operative inhaled nitric oxide (iNO), high frequency oscillation ventilation (HFOV) and extracorporeal membrane oxygenation (ECMO) compared to their counterparts [26].

NAVA has been associated with decreased sedative medication use [24, 25], including a significant reduction in the use of morphine and midazolam in neonates on invasive NAVA compared to a pre-NAVA period [25]. While neonates with CDH require sedation and analgesia following surgical repair, prolonged use of midazolam is correlated with adverse neurological outcomes including epileptiform activity, IVH and peri-ventricular leukomalacia [38, 39]. Furthermore, a retrospective analysis of 1,063 neonates with CDH from the Children's Hospitals Neonatal Database found both prolonged (over 5 days) opioid and benzodiazepine use was associated with increased mortality ($p<0.001$) and longer NICU stay ($p<0.001$).

Discussion

Studies have demonstrated the effectiveness of NAVA in aiding the transition from invasive ventilation to non-invasive respiratory support, by reducing PIP, MAP, FiO_2 and A-aDO_2, but its overall benefit for neonates with CDH remains unexplored [24, 27]. While theoretically, NAVA may reduce the duration of MV and hence VILI, long-term outcomes compared to conventional ventilatory strategies have yet to be investigated.

We recommend a multi-centre, prospective trial comparing NAVA with volume-controlled ventilation. Such a trial would be beneficial to evaluate both short and long-term outcomes of CDH infants managed with NAVA. In addition, given the cost of Servo ventilators, catheters and training personnel, a cost-effectiveness analysis would be important to evaluate the practicalities of implementing this ventilatory mode.

NAVA has been associated with a reduction in sedative medication use [24, 25]. This an important outcome as prolonged use of midazolam has been correlated with adverse neurological outcomes including epileptiform activity, IVH and peri-ventricular leukomalacia [38, 40]. This is hypothesised to be associated with a transient drop in mean arterial pressure and subsequent decrease in middle cerebral artery (MCA) flow [41]. A retrospective analysis of 1, 063 neonates with CDH from the Children's Hospitals Neonatal Database found both prolonged opioid and benzodiazepine use (over five days) was associated with increased mortality ($p<0.001$) and longer NICU stay ($p<0.001$) [38].

Research investigating NAVA in CDH infants is limited by small sample size studies [4, 24, 27]. This has been compounded by the exclusion of neonates who clinically deteriorate or failure to trigger the ventilator when placed on NAVA [25].

In conclusion, the current literature regarding NAVA in neonates with CDH is limited, making it difficult to form clinical recommendations regarding best standards of NAVA use. To our knowledge all research investigating invasive and non-invasive NAVA in neonates with CDH has focused on its post-operative implementation. Whether NAVA might be useful in CDH infants spontaneously breathing pre-operatively merits investigation.

Research funding: The research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Professor Greenough is currently receiving a non-conditional educational grant from SLE. A Servo n ventilator was loaned to us by Getinge – Maquet, Sweden. The company, however, have not been involved in data collection at KCH or St George's or in production of the manuscript.
Informed consent: Not applicable.
Ethical approval: Not applicable.

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