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ORIGINAL RESEARCH **NEONATAL ANESTHESIA**

Conventional mechanical ventilation versus high-frequency oscillatory ventilation in congenital diaphragmatic hernia of neonates: a systematic review

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Abstract

Background: Neonates with congenital diaphragmatic hernia (CDH) present with respiratory distress and circulatory insufficiency, requiring immediate intubation and mechanical ventilation. Studies in the literature present contradictory results regarding the optimal ventilation mode for neonates with congenital diaphragmatic hernia. We present a systematic review of the selected literature regarding high-frequency oscillatory ventilation (HFOV) compared to conventional mechanical ventilation (CMV) in congenital diaphragmatic hernia.

Methodology: PubMed, SCOPUS, EBSCOhost, and ProQuest databases were used to identify literature regarding HFOV compared to CMV in a CDH. The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and the Joanna Briggs Institute critical appraisal tool for randomized clinical trials. The search was conducted between the 23rd of October 2020 to November 2020. Articles that were included were published within the last twenty years (2000−2020). The following search and Boolean terms were used for the search of relevant articles: “Congenital Diaphragmatic Hernia” AND “high frequency” AND neonate AND “conventional mechanical ventilation”.

Results: Four studies were identified and considered eligible for the study. One study was a randomized clinical trial, and the other three cohort studies. Patients in the high-frequency oscillatory (HFO) group presented with a higher length of ventilation and hospital stay. There was a lack of evidence regarding any significant difference in the mortality rate.

Conclusion: We cannot make an evidence-based recommendation regarding the superiority of either CMV or HFOV as the optimal ventilation method in neonates with CDH. However, almost all studies observed a lengthened period of ventilation and time required before surgical repair in the HFOV group.

Abbreviations: CDH: congenital diaphragmatic hernia; CLD: chronic lung disease; CMV: conventional mechanical ventilation; GER: gastroesophageal reflux; HFOV: high-frequency oscillatory ventilation; NOS: Newcastle-Ottawa Scale; RDS: respiratory distress syndrome

Key words: Congenital Diaphragmatic Hernia; Conventional Mechanical Ventilation; High-Frequency Oscillatory Ventilation; Newcastle-Ottawa Scale; Ventilation

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1. Introduction

Congenital diaphragmatic hernia (CDH) is a congenital birth defect where a defect in the diaphragm allows herniation of abdominal contents into the thoracic cavity, interfering with normal development of the fetus, presenting as pulmonary hypoplasia and pulmonary hypertension.[1] Subsequently, neonates with CDH often present with respiratory distress and circulatory insufficiency. CDH occurs in 1 in 2000−5000 live births with a survival rate of 69−80%.[2–4]

High-frequency oscillatory ventilation (HFOV) is a ventilation strategy that employs a small tidal volume delivered rapidly (300−1500 breaths per minute) alongside a continuous distending pressure that maintains lung expansion.[5] The small tidal volume prevents ventilator-induced lung injury due to less volutrauma while providing adequate ventilation. HFOV is commonly indicated in patients with severe respiratory failure when conventional ventilation settings approach harmful parameters. In neonates, HFOV is frequently used as rescue therapy for respiratory failure from several conditions, which include respiratory distress syndrome (RDS), persistent pulmonary hypertension (PPHN), meconium aspiration syndrome (MAS), and congenital diaphragmatic hernia (CDH).

The Canadian Congenital Diaphragmatic Hernia Collaborative guideline on management of CDH recommends conventional ventilation as the primary mode of ventilation, with HFOV reserved as rescue therapy in neonates who do not meet ventilatory targets with conventional ventilation.[6] Although commonly indicated as rescue therapy, some centers have preferred HFOV as a primary ventilation mode in neonates with respiratory failure. A review by Henderson et al. comparing HFOV to conventional ventilation in neonates with predominantly RDS showed that neonates treated primarily with HFOV had a lower rate of chronic lung disease.[7] Migliazza et al. conducted a retrospective study where the use of primary HFOV in CDH presented a low rate of pulmonary morbidity.[8] Only one randomized clinical trial, the VICI trial, compared the use of HFOV and conventional ventilation in CDH. Results show no significant difference between the primary outcomes, mortality, and pulmonary morbidity between the two groups. However, secondary outcomes favor the use of conventional ventilation.

This study aims to compare the mortality rates in neonates with CDH between the use of HFOV and conventional ventilation, analyzing the contradicting results in current literature.

2. Methodology

PubMed, SCOPUS, EBSCOhost, and ProQuest databases were used to identify literature regarding HFOV compared to conventional mechanical ventilation (CMV) in a congenital diaphragmatic hernia. The search was conducted between the 23rd of October 2020 to November 2020. Articles that were included were published within the last twenty years (2000−2020). The following search and Boolean terms were used for the search of relevant articles: “Congenital Diaphragmatic Hernia” AND “high frequency” AND neonate AND “conventional mechanical ventilation”.

All articles identified from the search were assessed for their suitability by the pre-defined inclusion and exclusion criteria. Inclusion criteria were as follows; 1) written in English, 2) study participant was neonates with a congenital diaphragmatic hernia diagnosis confirmed, and 3) provided mortality/survival rates. Studies were excluded based on the following criteria; 1) the study was conducted on animals or in-vitro, 2) the study design was a case report, case series, or systematic review, 3) full text was not available. The following information was extracted from the included articles;

1) data of the study participants, where possible, include gestational age, birth weight, gender, location of CDH, associated congenital abnormalities, antenatal diagnosis, and APGAR score.

2) Methodology, which includes; setting and type of ventilator, treatment protocol (which includes the method of delivery), and intravenous (IV)/inhalational drugs administered.

3) The outcome of mortality rate, time to surgery, length of stay, period of ventilation, and complications. 4) Statistical analysis of mortality rates between the two treatment groups

Cohort studies used in this review were assessed for their quality using the Newcastle-Ottawa Scale (NOS).[9] The NOS assesses cohort studies through three different major categories, *Selection*, *Comparability*, and *Outcome*. A maximum of one star can be given for each criterion in *Selection* and *Outcome*, while a maximum of two stars can be given for *Comparability*, giving a possible maximum score of 9 stars. The study quality

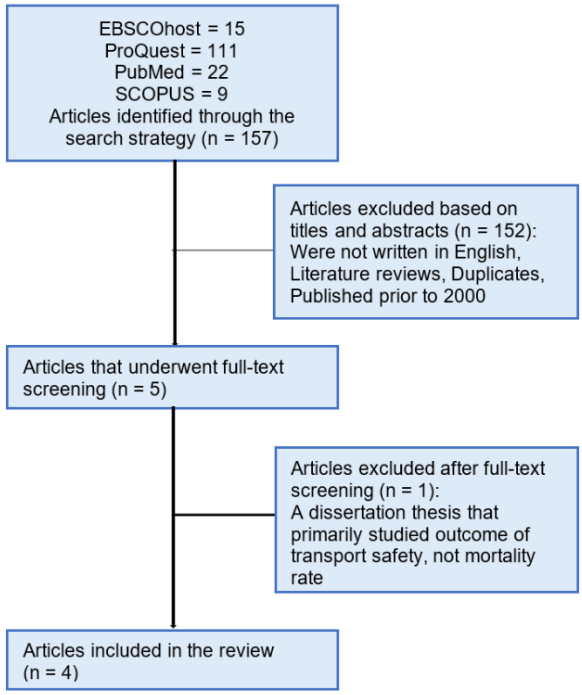

Figure 1: PRISMA flow diagram of study design

is determined by the number of stars obtained, 9 for excellent, 7–8 for good, 4–6 for adequate, and 1–3 for poor. Randomized clinical trials were assessed using the Joanna Briggs Institute (JBI) critical appraisal tool.[10] The JBI critical appraisal tool for RCTs includes 13 items in which to assess the trustworthiness and relevance of the paper.

Assessment of the quality of the papers was conducted by two independent reviewers individually. A third reviewer was then involved in the final assessment when the two independent reviewers had conflicting assessment points.

3. Results

The search strategy identified a total of 157 studies. The search terms resulted in 15, 111, 22, and 9 articles in EBSCOhost, ProQuest, PubMed, and SCOPUS databases, respectively. Out of the 157 studies, 152 studies were excluded based on the exclusion criteria. Five articles were identified to be potentially suitable, and a full-text review was conducted. Out of the five articles, one article was excluded as it was a dissertation thesis that studied the primary outcome of transport safety, not mortality. A total of four articles were identified to meet the inclusion criteria and considered appropriate for the review. Three of the articles were cohort studies, one a randomized controlled trial, and no studies were included from repeated searches.

All four of the included studies studied the survival or mortality rate between HFOV and CMV in neonates with CDH. In addition to mortality, Snoek et al. and Ng et al. included the development of bronchopulmonary dysplasia (BPD) or CLD respectively in neonates with CDH.[11,12] While Cacciari et al. and Desfrere et al. also aimed to study respiratory parameters using the two ventilation modes.[13,14] Study population characteristics can be found in Table 1. The mean gestational age of the participants was similar in both groups for all studies at 38 weeks. There were also no significant differences between birth weight, gender, and presence of associated congenital abnormalities. Neonates who received CMV in Cacciari had a higher rate of left-sided CDH, 96%, compared to the HFOV group, 79%, albeit no statistical analysis was given.

In Cacciari, neonates who underwent HFOV therapy had a significantly lower APGAR score at 5 min compared to neonates in the CMV group (5.6 ± 1.8 to 6.8 ± 1, $P < 0.008$). Only Snoek and Desfrere had the entire study population antenatally diagnosed, while the rest did not.

The survival rate of CDH with CMV in the articles from this review ranged from 38.0% to 56.0%. While with HFO, the survival rate ranged from 53.8% to 79.0% (Table 2). Ng (73% vs 38%, $P = 0.01$) and Desfrere (65.6% vs 26.3%, $P < 0.02$) reported significantly better survival rates with HFOV compared to CMV. Cacciari also reported a higher survival rate with HFOV (79% vs. 56%), but no statistical analysis was given. Only Snoek reported no significant difference between the survival rates of CMV and HFOV. All four articles included in this review reported a significantly longer time required for surgery in the HFOV group compared to the CMV group. Ng, Desfrere, and Cacciari reported a higher length of stay in survivors for the HFOV group, albeit not statistically significant. The HFOV treatment group was found to be ventilated for a longer period in Desfrere, Cacciari, and Snoek, and the difference was statistically significant (Table 2).

Ng and Snoek did not include data regarding the incidence of complications. Desfrere reported a higher incidence of pleural effusion (53% vs. 5.2%) and chronic lung disease (CLD) (14% vs. 0%) in the HFOV group compared to the CMV group. Both Desfrere and Cacciari reported a higher rate of pneumothorax in the CMV group, 31.6% to 18.8% in Desfrere and 32% compared to 10% in Cacciari.

4. Discussion

The neonatal resuscitation guideline from the American Heart Association recommends immediate endotracheal intubation in neonates with CDH.[15] After intubation, the Canadian Congenital Diaphragmatic Hernia Collaborative (CCDHC) guideline on diagnosis and

Table 1: Study population characteristics

	CMV	HFOV	p-value
Gestational age (weeks)			
Ng et al. (2008)	38.0 ± 1.6	37.7 ± 2.7	0.62
Desfrere et al. (2000)	37.6 ± 2.7	37.9 ± 1.9	NS
Cacciari et al. (2001)	38.1 ± 0.9	37.6 ± 0.9	NS
Snoek et al. (2016)	38.1 (37.4−38.9)	38 (37.3−39.0)	0.39
Birth weight (grams)			
Ng et al. (2008)	3011 ± 584	3051 ± 686	0.82
Desfrere et al. (2000)	2940 ± 800	2980 ± 600	NS
Cacciari et al. (2001)	2900 ± 500	2900 ± 400	NS
Snoek et al. (2016)	2950 ± 460	2890 ± 470	0.38
Gender, % of male			
Ng et al. (2008)	57%	57%	0.98
Desfrere et al. (2000)	NS	NS	NS
Cacciari et al. (2001)	60%	58%	NS
Snoek et al. (2016)	52.7%	45%	0.36
Left-sided CDH			
Ng et al. (2008)	71%	77%	0.61
Desfrere et al. (2000)	94.1%	91.7%	NS
Cacciari et al. (2001)	96.0%	79.0%	NS
Snoek et al. (2016)	82.4%	91.3%	0.12
Presented with associated congenital abnormalities			
Ng et al. (2008)	19%	16%	0.75
Desfrere et al. (2000)	42.1%	37.5%	NS
Cacciari et al. (2001)	12%	11%	NS
Snoek et al. (2016)	2.2%	3.7%	0.42
APGAR score 5 minutes			
Ng et al. (2008)	NS	NS	NS
Desfrere et al. (2000)	7.2 ± 1.9	8 ± 1.9	NS
Cacciari et al. (2001)	6.8 ± 1	5.6 ± 1.8	< 0.008
Snoek et al. (2016)	NS	NS	NS
Antenatal diagnosis			
Ng et al. (2008)	48%	68%	0.11
Desfrere et al. (2000)	100%	100%	N/A
Cacciari et al. (2001)	72%	73%	NS
Snoek et al. (2016)	100%	100%	N/A

Results presented as mean ± SD or median (IQR). CMV, conventional mechanic ventilation. HFO, high-flow oscillatory ventilation. NS, not specified. CDH, congenital diaphragmatic hernia. APGAR, appearance, pulse, grimace, activity and respiration.

management of CDH recommends gently, and intermittent mandatory ventilation should be the initial ventilation mode. HFOV is recommended to be used when the peak inspiratory pressure required to control hypercapnia using intermittent mandatory ventilation exceeds 25 cm H2O. The use of HFOV as a first-line

Table 2: Outcome of studies included

	CMV	HFOV	p-value
Survival			
Ng et al. (2008)	38.0%	73.0%	0.01
Desfrere et al. (2000)	26.3%	65.6%	< 0.02
Cacciari et al. (2001)	56.0%	79.0%	NS
Snoek et al. (2016)	76.9%	68.8%	NS
Time to surgery			
Ng et al. (2008) (in days)	5.0 ± 3.9	9.6 ± 11.5	0.04
Desfrere et al. (2000) (in hours)	6.5 (1−32)	96 (17−408)	< 0.0001
Cacciari et al. (2001) (in hours)	27.5 ± 22.9	37 ± 23.7	NS
Snoek et al. (2016) (in days)	4.0 (3.0−9.0)	5.0 (3.0−9.0)	0.005
Length of stay of survivors in days			
Ng et al. (2008)	25.2 ± 16.1	35.8 ± 44.8	0.94
Desfrere et al. (2000)	33 (28−45)	38.5 (15−360)	NS
Cacciari et al. (2001)	15.6 ± 11.7	28.2 ± 22.8	NS
Snoek et al. (2016)	23.0 (23.8−35.3)	20.0 (13.0−54.0)	0.99
Period of ventilation in days			
Ng et al. (2008)	18.7 ± 25.1	14.2 ± 20.4	0.94
Desfrere et al. (2000)	5 (3.5−9.0)	14 (4.0−901.0)	< 0.02
Cacciari et al. (2001)	8.2 ± 6.6	18.4 ± 9.1	< 0.0005
Snoek et al. (2016)	10.0 (6.0−18.0)	13.0 (8.0−23.0)	0.03

Results presented as mean ± SD or median (IQR). CMV, conventional mechanic ventilation. HFO, high-flow oscillatory ventilation. NS, not specified.

Table 3: Complications

	CMV	HFOV	p-value
Ng et al. (2008)	NS	NS	NS
Desfrere et al. (2000)	Pneumothorax: 6 (31.6%) Pleural effusion: 1 (5.2%) CLD: 0	Pneumothorax: 6 (18.8%) Pleural effusion: 11 (53%) CLD: 3 (14%)	NS
Cacciari et al. (2001)	Pneumothorax: 8 (32%) Pulmonary hypertension: 2 Intraventricular hemorrhage: 2 Caudate ganglion ischemia: 0 Intestinal obstruction: 1 GER: 1	Pneumothorax: 2 (10%) Pulmonary hypertension: 2 Intraventricular hemorrhage: 0 Caudate ganglion ischemia: 1 Intestinal obstruction: 1 GER: 2	NS
Snoek et al. (2016)	NS	NS	NS

CMV, conventional mechanic ventilation. HFOV, high-flow oscillatory ventilation. NS, not specified. CLD, chronic lung disease. GER, gastroesophageal reflux.

strategy for infants with CDH has been rising, with studies showing conflicting results. A thorough understanding of the optimal ventilation mode for neonates with CDH is required; hence we were prompted to conduct this review.

Of the three cohorts we identified, Ng and Desfrere were considered of adequate quality. Cacciari was considered good quality. All three studies had issues with comparability as the two treatment groups were not within the same time frame. Ng and Desfrere furthermore had the two treatment groups under different treatment protocols. The only RCT we identified was deemed good quality; no glaring issues were found with the study design and execution.

The study population in all of the four studies was found to be similar. One significant difference was found between the APGAR score after 5 minutes in Cacciari, where the HFOV group had a significantly lower APGAR score. Although the APGAR score is not primarily used to predict mortality, several studies have shown that a low APGAR score at 5 minutes is strongly associated with a higher risk of neonatal and infant death.[16,17]

Ng, Desfrere, and Cacciari all reported a higher mortality rate in the CMV group than the HFOV group, and the difference was found to be statistically significant, except in Cacciari, where the statistical analysis was not provided. Snoek also reported a higher mortality rate in the CMV group; however, the difference was not statistically significant. Ng, Desfrere, and Cacciari had the two treatment groups in two different periods, whereas all three had the HFOV treatment group in a more recent period. As is more recent, it can be assumed that the HFOV group received treatment from a more experienced center than the CMV group. Being more recent also can be assumed to come with better medical knowledge, more advanced medical equipment, better diagnostic tools, and treatments. The gentle ventilation with permissive hypercapnia was possibly less adopted in the earlier era. Cacciari explicitly states that both groups, although under different periods, underwent the same treatment protocol. At the same time, Desfrere and Ng had different treatment protocols for the two groups. In addition to the different ventilation modes, Desfrere also had different treatment protocols for the two groups. The CMV group had an emergency surgical repair, all of the subjects in the CMV group were transported to a pediatric surgery unit 1km away, and unstable infants were also transported. While the HFOV group had a delayed CDH repair, no unstable infants were transported, with some surgeries being performed in the NICU. In the Ng study, the treatment protocol for the treatment of pulmonary hypertension differed, and infants who underwent surgery were all performed using CMV. The CMV group received systemic prostacyclin, while the HFOV group received inhaled nitric oxide. Findings from these studies should be interpreted with caution as the higher mortality rates can be attributed to the different periods and treatment protocols, not solely due to the ventilation method.

Differing from the other three studies, Snoek et al., a randomized controlled trial, was the only one that reported neonates with CMV had a higher survival rate compared to HFOV. Snoek et al., known as the VICI trial was an international, multicenter study with 171 infants. Snoek's study however included both mortality or the occurrence of BPD as their primary outcome. When accounting for both mortality and BPD, 45.1% in the CMV group compared to 53.8% in the HFOV group, the statistical analysis performed showed no significant difference. None of the included patients was withdrawn and the primary outcome of mortality or BPD was observed for all. Out of 80 subjects in the HFOV group 32 remained under HFOV for the entirety of the study, 24 switched to CMV due to fulfilling predetermined failure criteria, and 24 converted to extracorporeal membrane oxygenation (ECMO). In the CMV group, 61 out 91 subjects remained with CMV, 14 switched to HFOV, and 16 converted to ECMO. HFOV had a 60% treatment failure rate while only 33% failed in the CMV group. Although an intention-to-treat analysis was performed, interpretation of the results should be taken into consideration with the fact that a significant number of subjects in both treatment groups received a different treatment protocol.

Across all studies, it was observed that there was a lengthened time to surgery and period of ventilation in the HFOV group. Only Ng observed the period of ventilation to be not significantly different between the two groups. The CCDH guideline[6] states that before surgery the following physiologic criteria should be met: 1) urine output > 1mL/kg/h, 2) FiO2 <0.5, 3) preductal oxygen saturation between 85% and 95%, 4) normal mean arterial pressure for gestational age, 5) lactate <3 mmol/L and 6) estimated pulmonary artery pressures less than systemic pressure. It should be noted that none of the studies in this article described the criteria of fitness for surgery in their study. Results in the Desfrere study should be interpreted with the fact that there were different treatment protocols in which the CMV group immediately underwent emergency surgery while the HFOV group had the CDH repair delayed.

Animal models have shown that HFOV improves pulmonary gas exchange, reduces barotrauma, and decreases inflammatory mediators.[18,19] It seems that animal models do not translate to neonates with CDH. Possible explanations hypothesized as to why HFOV causes the longer ventilation period may be attributed to

the more frequent suctioning, although not recorded, as pressures tend to be static in HFOV. Frequent suctioning may cause epithelium injury, hindering mucociliary clearance. Another proposed hypothesis is that HFOV creates a constant increased intrathoracic pressure which decreases venous return to the lungs, causing ischemia and increasing vulnerability to injury.[20] Dreyfuss et al.[21] observed that even with low tidal volumes, high levels of PEEP with constant tidal volume may exacerbate VILI. Patients receiving HFOV commonly require a higher amount of sedation and neuromuscular blockade which may lead to lengthier hospital stays.[22]

Complications were observed by two studies, Desfrere and Cacciari. Both studies showed that the CMV group presented with a higher pneumothorax rate than the HFOV group. HVOF employs lower tidal volume, which reduces the risk of barotrauma and volutrauma. Desfrere reported a higher number of pleural effusions in the HFOV group and that 8 out of the 12 pleural effusions found in the study were lymphatic. This finding was thought to be that the constant pressure during HFOV ventilation caused the higher intrathoracic pressure to contribute to fluid shifted to the intrathoracic cavity, additional to a lesion of the thoracic duct during surgery or abnormal development of lymphatic vessels as part of CDH.[23] Perhaps another explanation may be attributed to the lengthened ventilation duration in the HFOV group, as prolonged ventilation alters respiratory mechanics and impedes diaphragm contraction.[24,25]

We identified a relatively small number of relevant studies with limitations in study design and detailed methodology. Desfrere, Ng and Cacciari did not provide a sample size calculation; the results observed were perhaps not truly representative of the study population. While Snoek did not achieve the calculated sample size as the study was halted prematurely due to limited financial resources. Three articles had the two treatment groups in two completely different periods, e.g., Ng, Cacciari and Desfrere.[12,13,14]

5. Conclusion

Regarding the mortality rate, we cannot make an evidence-based recommendation regarding the superiority of either CMV or HFOV as the optimal ventilation method in neonates with CDH. However, almost all studies observed a lengthened period of ventilation and time required before surgical repair in the HFOV group. More studies, preferably randomized controlled trials, are needed to demonstrate the mortality rate, risks, and benefits of HFOV and CMV in neonates with CDH.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Conflict of interest

The author declare no conflict of interest, and no external or industry funding was involved.

9. Authors' contribution

CK, AAWR: Conceptualization, manuscript editing

RZ: Data collecting, data analysis, manuscript writing

RR, EH: Data analysis, Manuscript editing

RFS: Conceptualization, manuscript editing

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