The Role of Noninvasive Ventilation in Cystic Fibrosis: A Cochrane Review Summary With Commentary

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Background

One of the primary indications for noninvasive ventilation (NIV) is for the treatment of acute respiratory failure. NIV is often used in attempts to avoid tracheal intubation, and it is also commonly utilized for managing chronic respiratory failure in neuromuscular disease as well as other diagnoses in which progressive respiratory failure ensues. Additionally, NIV has been applied in obstructive sleep apnea when traditional treatment is inadequate in resolving apnea events. The use of NIV in individuals with cystic fibrosis has expanded beyond respiratory failure; it is also used as an adjunct therapy to airway clearance, as nighttime support for respiratory muscle weakness or fatigue, and as an aid to improve exercise tolerance. A 2017 Cochrane Review examined the use of NIV in cystic fibrosis during sleep, exercise, and airway clearance and considered its impact on outcomes such as quality of life, lung function, and gas exchange.[1]

New therapies and treatments over the past several decades have greatly improved outcomes for those with cystic fibrosis. Despite these advances in care, respiratory failure continues to be the leading cause of death for people with cystic fibrosis due to chronic lung infection and inflammation.[2] The purpose of this commentary is to discuss the published Cochrane Review, "Noninvasive Ventilation for Cystic Fibrosis,"[1] from a respiratory care perspective, produced under supervision of Cochrane Cystic Fibrosis and Genetic Disorders Group. Cochrane Corner is produced in agreement with RESPIRATORY CARE by Cochrane Rehabilitation.

What Is the Aim of This Cochrane Review?

The aim of this Cochrane Review was to evaluate the effects of using NIV in individuals with cystic fibrosis during exercise, during sleep, and as an airway clearance modality in comparison to no NIV.

What Was Studied in the Cochrane Review?

This review analyzed randomized controlled trials that compared outcomes with and without NIV use during sleep, during exercise, and for airway clearance in individuals with cystic fibrosis. The analysis included both children and adults with disease severity ranging from mild to severe. The primary outcome measures were mortality, quality of life, and symptoms of sleep-disordered breathing. There were 11 secondary outcomes: lung function, gas exchange, respiratory symptom scores and sputum production, exercise tolerance, impact on health resources, nocturnal polysomnography, nutrition and weight, right-sided cardiac function, cost, adherence to treatment and preference, and adverse events.

Up-to-Dateness of the Cochrane Review?

Studies published up to August 2016 were included by the authors of this review.

What Are the Main Results of the Cochrane Review?

The review identified 24 trials, of which 10 met inclusion criteria. There were 191 subjects with cystic fibrosis who utilized NIV either during sleep, with exercise, or for airway clearance. The age of study subjects ranged from 10 to 37 y with mild, moderate, or severe disease. Of the 10 trials, 6 evaluated NIV as an airway clearance modality ($n = 151$ subjects), 3 assessed NIV during sleep ($n = 27$ subjects),

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and 1 trial with 13 subjects examined the use of NIV with exercise. The duration of the selected trials varied, from a single treatment or a single night to 2 weeks, 6 weeks, or a period of 3 months. The evaluation of NIV use in subjects with cystic fibrosis revealed:

- NIV did not increase sputum production or expectoration compared to chest physiotherapy including directed cough (mean difference [MD] −0.69 g, 95% CI −3.06 to 1.67) (3 studies with 118 subjects) or to chest physiotherapy including positive expiratory pressure (MD −2.58 g, 95% CI −6.11 to 0.95) (1 study with 34 subjects).
- NIV is unlikely to improve FEV_1 compared to directed cough (MD −0.03 L, 95% CI −0.17 to 0.12) (2 studies with 43 subjects), positive expiratory pressure (MD −0.05 L, 95% CI −0.22 to 0.12) (1 study with 17 subjects), or to all airway clearance therapies (as measured by percent of predicted FEV_1) (MD 1.3%, 95% CI −7.32 to 9.92) (1 study with 40 subjects).
- Nighttime NIV compared to breathing room air without NIV may reduce transcutaneous carbon dioxide during rapid eye movement (REM) sleep (MD −0.9 mm Hg, 95% CI −1.62 to −0.18) and non-REM sleep (MD −0.7 mm Hg, 95% CI −1.15 to −0.25) (1 study with 6 subjects).
- Nighttime NIV may decrease minute ventilation during REM sleep compared to oxygen without NIV (MD 1.48 L/min, 95% CI 0.75–2.22) and room air (MD 1.56 L/min, 95% CI 0.05–3.07) (1 study with 13 subjects).
- Nighttime NIV does not improve percent of predicted FEV_1 when compared with oxygen (MD 1.0%, 95% CI −8.13 to 10.13) or with room air (MD 1.0%, 95% CI −8.62 to 10.62) (1 study with 8 subjects).
- NIV did not make a difference in quality of life with regard to the physical domain (MD −4.00, 95% CI −20.05 to 12.05) or the health domain (MD 3.00, 95% CI −12.52 to 18.52); however, NIV improved the respiratory domain (MD 3.00, 95% CI −12.52 to 18.52) when used as an airway clearance modality (1 study with 40 subjects, measuring quality of life using a questionnaire specific to cystic fibrosis).
- There were no studies evaluating mortality.
- Among the 5 studies making comments on adverse events, 2 studies reported no adverse effects of the intervention and 3 studies reported adverse events such as a withdrawal during respiratory testing at the onset of the study due to pain, intolerance to increases in inspiratory positive airway pressure (1 subject) or NIV mask (1 subject), pneumothorax (considered as coincidental) (1 subject), and aerophagia (2 subjects).

What Did the Authors Conclude?

The authors of this review concluded that the evidence to support NIV for treatment in individuals with cystic fibrosis is limited and that long-term multicenter trials are needed to better understand the role NIV may have on disease progression. While the data did not show any meaningful improvements in lung function when used for airway clearance, NIV might be helpful for selected individuals who experience fatigue, muscle weakness, or have difficulty with sputum expectoration. The potential benefits of NIV during exercise are uncertain because the available data are inadequate to make a determination. The greatest benefit was observed when NIV was applied during sleep for both single-treatment sessions as well as longer periods of time up to 3 months. However, these benefits did not seem to result in daytime improvements.

What Are the Implications of the Cochrane Evidence for Respiratory Care Practice?

Airway clearance therapy is considered one of the primary treatments for managing lung disease in individuals with cystic fibrosis.[3] Comparison studies of airway clearance modalities have not identified any individual therapy as superior to others.[3] The therapy of choice is often individualized and depends upon user preference, adherence, and whether the therapy improves airway clearance. This might best be individualized with an *n*-of-1 trial. FEV_1 has long been the accepted standard for monitoring cystic fibrosis lung disease severity and response to treatment.[4] The use of NIV as an airway clearance method did not improve FEV_1 or increase sputum in the 6 trials that evaluated this modality. Most of these trials were single-treatment studies, and only 1 trial evaluated participants for up to 2 weeks during a hospitalization for exacerbation. Directed cough and positive expiratory pressure were the most commonly compared airway clearance therapies, and only 1 trial compared NIV to all types of airway clearance, including chest physiotherapy. While NIV may not improve lung function outcomes, it could potentially have a role as an adjunct therapy to other airway clearance therapies, namely for those individuals with moderate to severe lung disease who experience respiratory muscle weakness, fatigue, or difficulty with sputum expectoration. However, this must be evaluated in appropriately powered, multicenter, randomized controlled trials before routine use.

Regular exercise is encouraged for people with cystic fibrosis to promote clearance of airway secretions and to improve lung function. Only 1 trial evaluating NIV during

exercise was identified by the authors. The study included a small number of subjects with mild, moderate, and severe lung disease and consisted of a 6-min walk test with and without NIV. No differences were found in lung function, sputum production, gas exchange, or exercise tolerance. Increased walk distance was reported, but the statistical significance of this is unclear because the original report noted significance ($P = .039$), whereas the Cochrane Review analysis did not (MD 28.6 m, 95% CI −34.04 to 90.95). Due to the limited data available, further study is needed to evaluate the use of NIV in this capacity to determine if there is any potential benefit.

The evaluation of nighttime NIV included 3 trials with a study duration ranging from a 1-night session to 6 weeks. Nocturnal NIV used with oxygen was noted to improve gas exchange during sleep in those with moderate to severe disease as compared to oxygen alone. This is not surprising because NIV is a proven treatment for chronic respiratory insufficiency and the natural progression of cystic fibrosis lung disease involves ensuing bronchiectasis and ultimately respiratory failure. What was interesting is that the positive effects were not carried over to daytime, as evidenced by neither daytime hypercapnia nor sleep architecture being affected by NIV during sleep in the longer 6-week trial. FEV_1 was not improved with nighttime NIV in any of the trials. However, improvements were seen with minute ventilation during REM sleep.

In general, NIV during sleep seems to offer the most potential benefit for individuals with cystic fibrosis compared to NIV with exercise or airway clearance. The review concludes that a single session of nighttime NIV improves the initial indicators of respiratory failure in cystic fibrosis, whereas longer use improves nocturnal hypercapnia, certain elements of quality of life, and exercise tolerance. NIV with airway clearance may help maintain or improve muscle strength, but there is not enough evidence to support the routine use of NIV as an adjunct to airway clearance or during exercise, although individual cases may possibly see a benefit. Consideration should be given to the degree of lung disease and longer duration of treatment in future studies.

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REFERENCES

1. Moran F, Bradley JM, Piper AJ. Non-invasive ventilation for cystic fibrosis. Cochrane Database Syst Rev 2017;2:CD002769.
2. Goetz D, Ren CL. Review of cystic fibrosis. Pediatr Ann 2019;48(4):e154-e161.
3. Flume PA, Robinson KA, O'Sullivan BP, Finder JD, Vender RL, Willey-Courand D-B, et al. Cystic fibrosis pulmonary guidelines: airway clearance therapies. Respir Care 2009;54(4):522-537.
4. Stanojevic S, Ratjen F. Physiologic endpoints for clinical studies for cystic fibrosis. J Cyst Fibros 2016;15(4):416-423.