Effects of inhaled furosemide on dyspnea and pulmonary function in people with COPD: A literature review

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Purpose: To determine whether inhaled furosemide can be effectively used in patients with chronic obstructive pulmonary disease (COPD) to improve feelings of dyspnea and improve pulmonary function values.

Methods: This literature review was conducted using randomized control trials and a literature review in which the participants consisted of or included patients with COPD receiving inhaled furosemide as a potential treatment option for their dyspnea and low pulmonary function values.

Results: Searches in four databases and secondary sources using five key terms yielded 83 unduplicated articles. Ultimately, four studies, one of which was a literature review, were included which studied the short-term result of inhaled furosemide on dyspnea and pulmonary function values. All studies measured dyspnea as an outcome and three found a statistically significant improvement in patient reported symptoms. Pulmonary function values were measured in all studies which all found improvements.

Conclusion: The effect of inhaled furosemide on the dyspnea and pulmonary function values in people with COPD remains uncertain, and questions have emerged regarding the long-term impact on these patients. While this therapy is promising for dyspnea relief and improvement of pulmonary function values in people with COPD, further consideration and additional data still need to be gathered.

Key Words: *inhalation administration; furosemide; COPD; literature review; dyspnea*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease throughout the world that is preventable and treatable. COPD is estimated to the cause of 3 million deaths worldwide every year [1]. COPD is characterized by airflow obstruction, frequent respiratory symptoms, and airway/alveolar abnormalities. One of the most common and evident respiratory symptoms of COPD is dyspnea [2]. Dyspnea is any difficult or labored breathing and can be detrimental to the quality of life (QOL) of patients with COPD [2]. Finding ways to try to alleviate the discomfort in breathing is essential for improving patients' QOL. The difficulty with quantifying the sensation of dyspnea is that it is experienced differently among patients and may be caused by a multitude of factors, such as muscle fatigue and patient perception. Dyspnea is commonly measured using the subjective comments of the patient (such as the visual analog scale and the numerical rating scale) [3].

A visual analog scale is commonly used to assess dyspnea during exercise testing and requires the subject to quantify their feeling of dyspnea using a scale ranging from "no breathlessness" to "intolerable breathlessness" [4]. The numerical rating scale is similar in its purpose; the scale ranges from 0 = no breathlessness to 10 = worst breathlessness possible. Both scales are validated but neither have been preferentially adopted specifically for dyspnea assessment in COPD patients [5].

However, a more objective method is analyzing the pulmonary function values. In a patient with COPD, pulmonary function values such as forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and peak expiratory flow rate (PEFR) are linked to the severity of their symptoms and confirms the presence of airflow obstruction [6]. It should be noted that according to the Global Initiative for Chronic Obstructive Lung Disease [2], the correlation between pulmonary function values and symptoms is not strong; thus, assessment of the patient's subjective dyspnea score is essential for assessing the patient's stage of COPD properly [6].

There is some evidence that shows that inhaled furosemide, a common loop diuretic, may be useful in relieving dyspnea in patients with COPD [7]. The mechanism of action of this potential therapy is not yet fully understood; however, it has been suggested that inhaled furosemide acts with a bronchodilator effect on the airway epithelium [7]. Inhaled furosemide has also been evaluated in studies with relation to asthmatic patients, terminally ill patients, and neonates with lung diseases [8–10]. Nevertheless, even with the current studies on the potential benefits of inhaled furosemide, the clinical evidence is lacking to support its use as a therapy. Further research is essential to investigate whether this therapy can be used to improve feelings of dyspnea in patients and what the mechanism of action is. The research question for this literature review, therefore, was "In people with COPD, does inhaled furosemide lead to decreased perception of dyspnea and improved pulmonary function values?"

METHODS

Identification of studies

This literature review does not have a review protocol or registration number. The review consists of three randomized control trials (RCTs) and a literature review investigating the effect of inhaled furosemide on dyspnea and pulmonary function values in patients with COPD. Studies were excluded if these outcomes were studied in general with no relation

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TABLE 1

Cochrane risk of bias assessment tool for included randomized control trials

Study	Vahedi et al. [12]		Saba et al. [13]	Masoumi et al. [14]
Random sequence generation	Low risk		Low risk	Low risk
Allocation concealment	Low risk		Low risk	Low risk
Blinding—participants and personnel	Low risk		Unclear risk	Unclear risk
Blinding—outcome assessment	Low risk		Unclear risk	Low risk
Incomplete outcome data	Low risk		Low risk	Low risk
Selective reporting	Low risk		Low risk	Low risk
Other bias	High risk of baseline imbalance. Baseline FEV_1 was higher in the furosemide group.		Low risk	Low risk

to COPD or if inhaled furosemide was not explicitly studied in relation to dyspnea and pulmonary function.

Outcome measures

The outcome measures were pulmonary function values (FVC, FEV_1, PEFR), and dyspnea perception (using either a visual analog scale or the numerical rating scale). The perception of dyspnea is clinically important when providing and assessing the effectiveness of therapies for people with COPD [2]. Additionally, pulmonary function values are the gold standard in diagnosing COPD and assessing any clinical changes in the patient [2].

Information sources

This literature review searched four electronic databases: PubMed (2010–2020), Cochrane Library (2010–2020), CINAHL (2010–2020), and EMBASE (2010–2020). Publication date limits were set for all databases from 2010 to 2020 to provide recent articles for the most applicable use in today's healthcare system. Additionally, citation tracking was also performed on all the documents identified. Google Scholar, Google, and the clinical trials registry at http://www.clinicaltrials.gov were searched using the terms "inhaled furosemide" and "'chronic obstructive pulmonary disease". Contact was made with authors of promising abstracts to obtain the full-text version; however, no author responded to share the full text. The last search was conducted on 24 February 2020.

Search strategy and assessment of studies

MeSH terms that were used to get the most comprehensive and concise searches in PubMed were inhalation, administration OR Inhal* OR aerosol OR insufflat* OR vapor* OR Nebuli* OR insufflat* AND Frusemide OR Fursemide OR Frusemid OR Fusid OR Lasix OR Furosemide OR Errolon OR Furanthril OR Furantral OR furosemide (see Supplementary materials[1] for the full PubMed search strategy).

Search limits were set to further improve the search, such as studies with a publication date in the last 10 years, human studies only, and published in English. Because of their high levels of evidence meta-analysis, systematic reviews, randomized controlled trials, and practice guidelines were primarily searched for in this study to reach a conclusion of what effect inhaled furosemide has on dyspnea and pulmonary function values in COPD patients. The title, abstract, keywords, and the body of the article were analyzed. After the search was conducted and the articles were filtered according to relevance and quality of evidence (using the Cochrane risk of bias assessment tool), the remaining articles were examined. Selected articles were included for full test screening and assessed based on study name, publication date, study design, sample size, participants, intervention, control, outcomes, and any conflict of interest. Additionally, the included studies were looked at to ensure they have a control group that received adequate standard care for COPD patients. The diagnosis of COPD was independently evaluated from spirometric and nonspirometric indices as per the gold standards [2].

This literature review was guided by the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) statement. Both the Consolidated Standards of Reporting Trials checklist and the Cochrane Collaboration Assessment of Risk of Bias of Included Studies Guideline were used to evaluate the assessment of bias of the included randomized control trials.

RESULTS

Study selection

As a result of the key terms and the limits used in this search, a total of 83 unduplicated results were discovered (see Figure 1). Twenty-five results were from PubMed, 58 results from Cochrane Library, 13 from EMBASE, and 18 from CINAHL. One result was obtained through citation tracking. Of these, 22 met the screening criteria and were assessed for eligibility. Eighteen full-text articles were excluded because they were descriptive articles (2), they were only abstracts (5), they studied dyspnea not in relation to COPD (9), and one was a book (1). The included articles were all published within the last 10 years and all studied inhaled furosemide use with COPD patients.

Characteristics of studies

Four publications are included in this literature review, with a total of 259 participants in the three RCTs alone. Participants all had a formal diagnosis of COPD. One of the studies (RCT) combined the classification of COPD with asthma, while the remaining RCTs and the literature review looked at COPD as an individual disease category. All the studies looked at the effect of inhaled furosemide on dyspnea and, while all publications examined the effect on pulmonary function values, the use of FEV_1, FVC, and (or) PEFR differed. It was noted there was some heterogeneity across publications regarding how dyspnea perception was measured; however, subjective testing was the conventional technique.

Critical analysis

The RCTs were assessed for risk of bias using the Cochrane Risk of Bias Assessment Tool as outlined in the criteria of the Cochrane Handbook for Systematic Reviews of Interventions [11]. The quality of the included RCTs ranges from having mostly low risk of biases to having an unclear risk of bias (due to inadequate detail) (see Table 1). To evaluate the quality of the literature review, PRISMA was used, which showed it to be a high-quality literature review that assessed the quality of its included studies using a strength of evidence rating system known as the "Grading of Recommendations, Assessment, Development and Evaluations" (GRADE) rating.

Effect of intervention

All studies assessed how inhaled furosemide influenced short-term dyspnea relief and short-term impact on pulmonary function values in people with COPD. Table 2 was used to summarize the included publications and assess what each study concluded.

Most publications found statistically significant improvement in dyspnea perception when inhaled furosemide was the intervention in question. Vahedi et al. [12] found that while dyspnea improved one hour after treatment in both the intervention group (furosemide 40 mg) and the placebo group (saline), the improvement for the intervention group was significantly greater and was statistically significant ($p < 0.001$, which

FIGURE 1

Prisma flowsheet.

COPD = Chronic obstructive pulmonary disease.
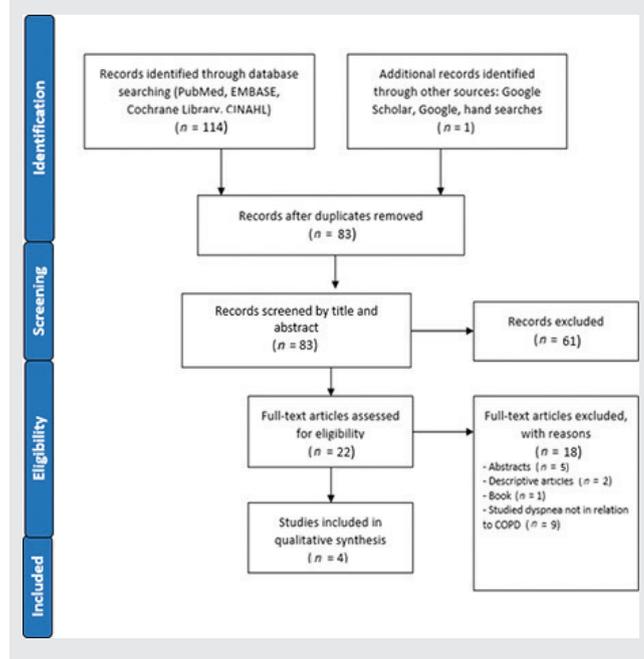
is less than 0.5 alpha level). Boyden et al. [15] similarly concluded that inhaled furosemide contributed to dyspnea relief in patients with COPD. Additionally, although Masoumi et al. [14] did not measure dyspnea as one of their outcomes, they did notice an improvement in the patient-reported severity of dyspnea post-inhaled furosemide intervention compared to just salbutamol.

Saba et al. [13] similarly showed that although the pulmonary function values improved in both treatment groups, the improvements were only significant when both treatments (salbutamol and inhaled furosemide) were given ($p < 0.001$). However, the dyspnea perception (BORG, a scale to measure dyspnea severity) improved significantly after just the first treatment of either salbutamol or inhaled furosemide. Additionally, the order of the drug administration did not significantly affect any of the outcomes. With a symptom such as dyspnea, which is so subjective, any clinical benefit that patients get is important to keep in mind.

Pulmonary function values (FEV_1, FVC, and PEFR) were assessed in three of the publications separately (not all in the same article). Vahedi et al. [12] noted significant improvement in FEV_1 of about 7% with inhaled furosemide (FEV_1 and dyspnea severity scores were recorded 1 h after treatment). Masoumi et al. [14] stated that mean PEFR in furosemide patients was significantly increased, from 336.98 ± 81.846 compared to a PEFR of 280.62 ± 84.384 in the salbutamol only group ($p = 0.001$). Lastly, the literature review by Boyden et al. [15] reported that the included studies indicated significant improvements in FEV_1 and FVC with inhaled furosemide.

DISCUSSION

Summary of main findings

The articles included in this literature review present a potentially significant effect of inhaled furosemide on dyspnea and significant effect on pulmonary function values in people with COPD. Two of the studies measured dyspnea as a primary outcome, whereas two measured various pulmonary function values as their primary outcome. Additionally, all publications assessed the temporary nature of inhaled

furosemide and the short-term impact on dyspnea and pulmonary function values, as opposed to any long-term effects. This has implications for clinical practice, clinicians, and policy makers as the possible systemic effects of inhaled furosemide cannot be confirmed using these studies.

Future research should consider the long-term impact of inhaled furosemide on dyspnea and pulmonary function values. Additionally, there are current theories of how inhaled furosemide works: one of those being the potential modulation of respiratory sensation by altering afferent inputs from vagal receptors in the lungs of people with COPD [16]. However, further research is still needed for it to be a treatment option for COPD patients. In the meantime, since inhaled furosemide has been shown to at least demonstrate a clinically significant improvement for COPD patients, researchers and clinicians should consider the use of inhaled furosemide in conjunction with current known COPD interventions to potentially alleviate patients' symptoms.

Quality of the evidence

The quality of the overall evidence from the RCTs was assessed using the Cochrane risk-of-bias assessment tool, which included assessment of random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. The assessment of the risk of bias in the included RCTs suggested that there was a range of low risk of bias to unclear risk of bias for each of the studies. For example, Vahedi et al. [12] demonstrated a low risk of bias in all but one aspect of the tool. The risk of other bias was high due to the presence of baseline imbalance; baseline FEV_1 was higher in the inhaled furosemide intervention group. This may affect results because the participants in this group have potentially less severe COPD symptoms or perhaps because they have a better capability to improve because of their better baseline values. However, this limitation was addressed in the RCT, and it was noted that even the inhaled furosemide group participants that had lower baseline FEV_1 had a significant improvement in their dyspnea perception [12]. Additionally, Saba et al. [17] demonstrated low, unclear risk in all categories excluding the selective reporting where high risk was identified because only stable COPD patients were selected with no exacerbations or hospital admissions in the last month. These criteria question the severity of COPD in these patients; therefore, when considering patients experiencing COPD exacerbations, optimal interventional may differ. Additionally, a general limitation of this literature review is that only articles up until 2020 were included.

Potential biases in the review process

There were no identified sources of bias in the review process.

Discussion in relation to other studies or reviews

Two RCTs that were done before 2010 should be considered when discussing this topic due to their impact. Jensen et al. [16] and Ong et al. [17] both examined the efficacy of inhaled furosemide in COPD patients. Ong et al. [17] concluded that inhaled furosemide provides relief for induced dyspnea in people with COPD (and results in bronchodilation). Additionally, it was noted that there was a significant improvement in mean FEV_1 and FVC after intervention with inhaled furosemide ($p = 0.038$ and $p = 0.005$, respectively). Furthermore, the percentage of FEV_1 improvement in this RCT was similar to what was noted by Vahedi et al. [12] (5% improvement versus 7% improvement with furosemide, respectively). Likewise, Jensen et al. [16] reported statistically significant alleviation of exercise-induced dyspnea in people with COPD following inhaled furosemide therapy.

However, it should be noted that the participants in both the RCTs included were clinically stable at the time (no recent exacerbation of symptoms). This differs from Masoumi et al. [14] and Vahedi et al. [12] as both RCTs included patients with COPD who presented to the emergency department with an acute exacerbation. The potential difference in significance between the two conditions of COPD patients should be

TABLE 2

Summary of included articles

Study	Participants	Intervention/Outcomes	Results
Vahedi et al. [12]; 5-month randomized double blinded clinical trial	n = 100 (63 males). Mean age 73.1 ± 8.7 years. All participants had COPD diagnoses, presented to emergency department with COPD exacerbation. Mean baseline FEV_1 was 53.8 ± 4.4% of predicted.	Primary outcomes: dyspnea severity (measured with a visual analog scale) and FEV_1. Intervention: received 40 mg (in 4 mL) nebulized furosemide or placebo as an adjunct to the conventional treatments.	Dyspnea and FEV_1 improved in both intervention and placebo groups, but the improvement was significantly greater in the intervention group ($p < 0.001$, which is less than 0.5 alpha level).
Saba et al. [13]; randomized double blind controlled trial	n = 69 (55 males). Mean age 64.92 ± 11.71 years.	Participants were divided into two groups. The first group received 5 mg salbutamol in their first episode while the second group received inhaled furosemide (40 mg) in their first episode. The treatments for the two groups were subsequently reversed. Spirometry values (FEV_1, FVC, and FEV_1/FVC) and dyspnea scores (BORG) were assessed as primary outcomes between episodes and after the second episode in both groups.	The primary outcomes improved in both groups after the first episode however only the BORG scale significantly improved after the first episode ($p < 0.001$). However, all outcomes improved significantly after the second episode in both groups ($p < 0.001$). The sequence of drug administration did not cause a significant effect as the two groups did not have significantly different reactions.
Masoumi et al. [14]; randomized, double blind, clinical trial	n = 90 (45 in each intervention group), 30 males total. Mean age in salbutamol group is 41.38 ± 10.798 years and mean age in salbutamol and furosemide group is 37.73 ± 10.116 years. Participants who were admitted to the emergency department with "possible" reactive airway disease (asthma/COPD) and acute exacerbation of symptoms were included.	Participants received 5 mg of nebulized salbutamol and 40 mg of nebulized furosemide in the intervention group and 5 mg of nebulized salbutamol alone in the control group. PEFR was estimated before treatment and at specific intervals after.	The difference between the mean PEFR of the two groups was significant at the end of the trial (p = 0.0001). Post-intervention, severity of dyspnea was noted to be worse in the salbutamol group than furosemide group.
Boyden et al. [15]; literature review.	Thirty-nine total publications. Search of Medline/ PubMed, CINAHL, Cochrane, and Google Scholar (1989 – 2013). Inclusion criteria included: examining the use of nebulized medications for the treatment of dyspnea related to COPD, and other pulmonary conditions.	Four of the studies in this review specifically looked at inhaled furosemide use with COPD participants. The dose used was between 20 mg – 40 mg depending on the study with one study using up to 160 mg.	A potential benefit was suggested for nebulized furosemide. Included studies indicated significant improvements in FEV_1, FVC, and dyspnea relief with inhaled furosemide.

Note: FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; PEFR = peak expiratory flow rate; COPD = Chronic obstructive pulmonary disease.

considered, because patients who are going through an acute exacerbation may show physiologically different responses.

Additionally, another article that should be considered is a systematic review and Meta-analysis by Ghaysouri et al. [18]. This review included and analyzed eight articles that looked at $PaCO_2$, heart rate, oxygen saturation (SpO_2), PEFR, and FEV_1. It was noted the PEFR and the FEV_1 in the patients receiving the inhaled furosemide were closer to the reference values that patients receiving the placebo (49 and 46.87, respectively).

CONCLUSION

Currently, inhaled furosemide is not a standard therapy for dyspnea relief and improvement of pulmonary function values in people with COPD. Evidence-based research is required to help determine the best way to integrate this research into current practice. To date, while the therapy of inhaled furosemide is promising for dyspnea relief and improvement of pulmonary function values in people with COPD, there is still insufficient data to draw definitive conclusions regarding the effectiveness of inhaled furosemide in this case.

DISCLOSURES

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