

Efficiency of Nebulizing Furosemide in the Treatment of Chronic Pulmonary Obstructive Disease: A Systematic Review and Meta-Analysis of Clinical Trials

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Background: Chronic obstructive pulmonary disease (COPD) is one of the most common chronic illnesses in humans. Among both oral and intravenous diuretics, nebulizing furosemide (Lasix) is the most commonly used agent. The purpose of this study was to ascertain the therapeutic effects of nebulizing furosemide compared with placebo in the treatment of COPD using a systematic review and meta-analysis of clinical trials.

Materials and Methods: This review was performed based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) protocol. The databases of Web of Science, Google Scholar, PubMed, and Scopus were independently searched by two researchers using MeSH keywords. Studies published between 2002 and 2018 in different parts of the world were considered. The meta-analysis was performed through STATA 14 software and the heterogeneity was assessed using Q statistic or I² index.

Results: From 40 selected articles, 8 articles were finally included in the systematic review process. The analyses were performed considering two groups; nebulizing furosemide treatment (i.e. case) and placebo (i.e. control). Based on the forest plots, the average values of PaCO₂ were 48.3 (39.04-57.56) and 46.56 (39.94 -53.18) in the case and control groups, respectively. Also, the mean forced expiratory volume in the first second (FEV1) was 49 (31.32-66.67) and 46.87 (31.44-62.30) in the case and control groups, respectively. Meta-regression analysis showed that both heart and pulse rates in the nebulizing furosemide group decreased by increasing the year of study and sample size (P <0.001). The heterogeneity among the studies was found to be 72.2%, which is classified as severe heterogeneity.

Conclusion: nebulizing furosemide can improve and normalize the vital signs and other respiratory variables in patients with COPD.

Key words: Nebulizing Furosemide; COPD; Meta-Analysis; Clinical Trial

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic obstructive lung disease with failures in breathing or dyspnea, airflow limitation, shortness of breath, sputum cough, and physical activity-related breathlessness, which

progressively exacerbate over time (1-2). This disease continues to be the leading cause of morbidity and mortality around the world with an enormous healthcare burden (3).

About 16 million Americans have been diagnosed with COPD, and the disease has been estimated as the sixth cause of death in the United States (4). In developing countries, such as Iran, the rate of mortality due to COPD has risen during the last 15 years (5).

The most common cause of COPD is smoking, but other factors, such as air pollution and hereditary factors may also contribute to this condition (5, 6). COPD is diagnosed based on the presentation of dyspnea in lung functional tests (2, 7). Collectively, for the diagnosis of COPD, a comprehensive clinical test, such as spirometry, chest radiography, complete blood count, and pulse oximetry are mandatory (8).

Patients with COPD have a broad range of respiratory symptoms and signs (8). However, the most common symptoms of COPD include sputum production, difficulty in breathing or breathlessness, and cough (7, 9). The management of COPD necessitates quitting smoking, pulmonary rehabilitation, using bronchodilators, maintenance of physical activity, administering corticosteroids, long-term oxygen therapy, and finally lung transplantation in some patients (10-12). The non-drug and drug interventions showed the same impacts on improving the quality of life and alleviating the symptoms and outcomes of COPD (13).

Regarding drug therapy, except oxygen, no drug has been accompanied by the reduced risk of mortality in patients with COPD. Therefore, drugs are predominately prescribed for improving the quality of life, reducing the disease symptoms, and improving the functional capacity of the lung (14).

A wide range of drugs, such as inhaled short-acting beta-agonist (15), long-acting muscarinic antagonist, and long-acting beta-agonist (16, 17) are currently used for the treatment of COPD, which is associated with adverse effects (13).

Among short-acting beta-agonists, nebulizing furosemide is the most common agent used for the treatment of COPD (18). Furosemide is also useful in the treatment of left ventricular dysfunction reducing central blood and capillary hydrostatic pressures (19). It has been

shown that the inhalation of furosemide in patients with stable COPD could relieve the dyspnea symptom and significantly improve bronchodilator during constant-load activities (20). Furthermore, in another study, it has been exhibited that the prescription of nebulized furosemide (40 mg) for COPD patients hampered COPD exacerbation (20). Despite the mentioned data, a more recent study by Waskiw-Ford et al. has questioned the effect of nebulized furosemide on exertional breathlessness in healthy men (21). In this study, the inhalation of furosemide at the doses of 40 and 120 mg did not relieve the breathlessness caused by endurance exercise test in normal men. Furthermore, optimal and controlled administration of nebulized furosemide did not create greater easement of breathlessness compared with placebo (aerosol saline) in healthy subjects (21, 22). The reason for these inconstances has not been strictly addressed; therefore, further investigations are needed.

The mechanism, by which inhaled furosemide relieves exertional dyspnea in COPD patients is multifactorial, but modulating the activity of pulmonary stretch receptors (23), which in turn alters pulmonary vagal afferent and improves airway function and dynamic ventilator (24) is also a contributory factor. Increasing the activity of the pulmonary vagal afferent by inhaled furosemide provokes larger tidal volume, leading to alleviating the sensation of breathlessness (25). It seems that the benefits of furosemide in dyspnea for COPD may outweigh its adverse effects, but further studies are required (4).

Drug delivery by nebulizers is a method for administering non-inhalable medications (26). Regarding furosemide, although intravenous delivery has been able to reduce breathing discomfort, nebulizers are more effective (22). Nebulizer application depends on features, such as particle size, shape, and density, surface tension, and the anatomy of the respiratory system (21). The main advantage of nebulizers is obviating the need for drugs to be digested and pass into the blood circulation; therefore, they are rapidly absorbed through the respiratory system (27).

The aim of meta-analysis studies is to provide a comprehensive and integrated approach regarding a specific subject (28, 29). No meta-analyses have yet been done on the clinical trials assessing the therapeutic effects of furosemide in patients with COPD. Additionally, knowledge obtained from the aforementioned studies cannot provide a definite result for COPD in a clinical setting. Considering numerous studies in this field, and in order to validate the results of these studies, we compared the therapeutic effects of furosemide and placebo in patients with COPD through a systematic review and meta-analysis on clinical trials.

MATERIALS AND METHODS

This systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The five steps followed in this study included the initial design, literature search, collection and evaluation of articles, qualification of articles, and finally data analysis. In order to prevent publication bias, the search was independently conducted by two researchers, and the results of the studies were combined by a third scholar.

Search strategy

A comprehensive search was independently performed by two researchers using the national and international scientific resources (Magiran, Iran Medex, PubMed, Cochrane, Web of Science, and Scopus), as well as the Google scholar search engine to obtain the literature related to the research question. Accordingly, nebulizing furosemide, placebo, and COPD keywords were first used individually, and then in combination, to perform a comprehensive search. In the end, all references of the articles were also searched to find relevant articles. To select relevant articles and exclude duplicated ones, the full texts of the articles were provided to the researchers.

Inclusion criteria

The clinical trials comparing the therapeutic effects of nebulizing furosemide and placebo in patients with COPD were included.

Exclusion criteria

Low-quality studies, irrelevant articles, studies with inadequate data, reviews, case reports, letters to editors, qualitative studies, and abstracts of congress papers that contained incomplete information were excluded.

Screening and qualifying the studies

The STROBE checklist was used to evaluate the quality of the articles (21, 27). Two authors individually scored each part of the checklist between 0 and 2. Based on the scores obtained from the checklist, the quality of the articles was divided into three groups as weak, moderate, and good with scores of 1-15, 16-30, and 31-44, respectively. Articles that obtained a good score of at least 16 entered into the meta-analysis process.

Measurement tools used in the articles

Studies that compared the therapeutic effects of nebulizing furosemide versus placebo in patients with COPD were systematically reviewed and included in the meta-analysis process.

Data extraction

The collected data from each article included the first author's name, the year and location of the study, sample size, and the therapeutic effects of nebulizing furosemide and placebo. The outcomes included changes in the vital signs (i.e. respiratory rate, blood pressure, and heart rate) and respiratory parameters (i.e. PaCO₂, PaO₂, HCO₃, pH, forced expiratory volume in the first second (FEV1), peak expiratory flow rate (PEFR), and SaO₂). The obtained data were recorded in a checklist designed by the researcher.

Statistical analysis

Given the type of the data extracted and the number of final included studies (i.e. less than 10), the publication bias was not assessed, and a funnel plot was not drawn. The I-squared (I²) index was used to calculate the heterogeneity among the studies for each variable, including the vital signs (i.e. respiratory rate, blood pressure, and heart rate) and respiratory parameters (i.e. PaCO₂, PaO₂, HCO₃, pH, FEV1, PEFR, and SaO₂).

Considering the significant heterogeneity among the studies ($P < 0.001$), a meta-analysis was conducted using a random-effects model to combine the results of different studies. The data were analyzed using STATA software version 14.

RESULTS

At first, a list of all the titles and abstracts of the selected articles was prepared. After hiding the specifications of the articles, including the names of the journals and authors, the full texts of the articles were provided to the researchers. In the initial search, 40 articles related to the subject were obtained, of which 20 articles were omitted due to the lack of proper communication and inadequate results. Finally, by reviewing the full texts of the articles, 12 additional studies were omitted due to not fulfilling the inclusion criteria. At last, eight articles were evaluated and entered into the meta-analysis phase. The steps of the study selection are shown in Figure 1.

Totally, 465 patients with COPD had been analyzed with a mean sample size of 58 patients in each study. The characteristics of the articles and their findings on the therapeutic effects of nebulizing furosemide in the treatment of COPD are provided in Table 1. Comparison of the vital signs between the two study groups showed that patients treated with nebulizing furosemide had values closer to normal (Table 2). The respiratory parameters in the two study groups are provided in Table 3. The results showed that patients who had received nebulizing

furosemide had respiratory values closer to the normal levels indicating good therapeutic efficacy for this agent.

Table 1. The specifications of the studies comparing the therapeutic effects of nebulizing furosemide and placebo in patients with COPD

References	Author	Year	Place	N Total
30	Vahedi, et al.	2013	Iran	100
31	Brijker, et al.	2002	Netherlands	20
32	van de Ven, et al.	2002	Netherlands	70
21	Waskiw-Ford, et al.	2018	Canada	24
33	Zhang, et al.	2012	China	60
34	Alshehri, et al.	2005	Saudi Arabia	60
35	Masoumi, et al.	2014	Iran	90
36	Panahi, et al.	2008	Iran	41

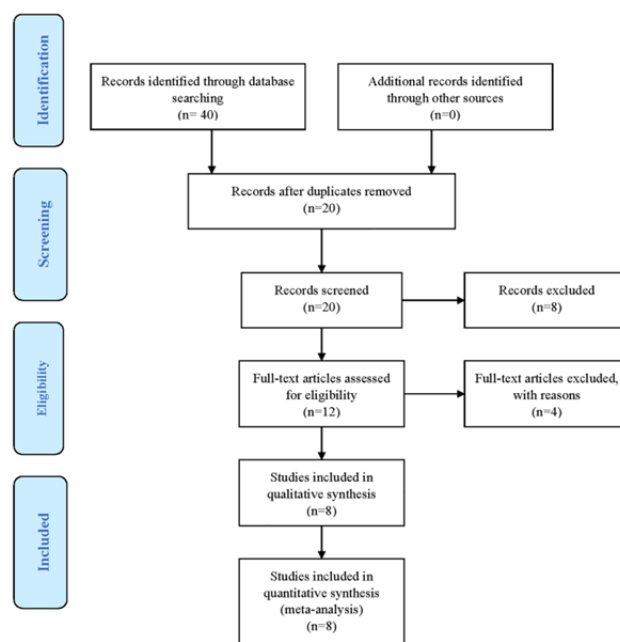


Figure 1. Flowchart of the present systematic review and meta-analysis

Table 2. Comparison of vital signs between the two studied groups

Group	Vital signs	Articles(N)	Mean	CI/95	I ²	P Value
Case group	Respiratory Rate	3	17.82	13.44-22.20	78.2	0.000
Control group	Respiratory Rate	3	19.98	14.13-25.84	57.2	0.121
Case group	Blood Pressure	2	10.23	8.68-11.78	0	0.647
Control group	Blood Pressure	2	10.51	9.29-11.73	0	0.932
Case group	Heart Rate	4	77.5	72.18-82.82	0	0.710
Control group	Heart Rate	4	83.78	69.11-98.44	81.2	0.001

Figure 2 shows the forest plot of PaCO₂ in the case (Figure 2a) and control (Figure 2b) groups with the mean values of 48.3 (39.04-57.56) and 46.56 (39.94 -53.18), respectively. Figure 3 displays the forest plot of FEV1 in the case (Figure 3a) and control (Figure 3b) groups with the mean values of 49 (31.32-66.67) and 46.87(31.44-62.30), respectively. The meta-regression analysis based on the

year of study showed that the heart rate decreased with an increase in the year of study (P <0.001) while it increased in studies with larger sample sizes (P <0.001, Figure 3). Also, pulse rate significantly decreased by increasing in the study year and sample size (P <0.001, Figure 4). The heterogeneity among the studies was 72.2%, which is considered as a high heterogeneity (28, 29).

Table 3. Comparison of respiratory parameters between the two studied groups

Group	Parameters	Articles(N)	Mean	CI/95	I ²	P Value
Case group	PH	3	7.41	7.35-7.47	59.4	0.085
Control group	PH	3	7.38	7.38-7.45	64.6	0.059
Case group	Pa CO2	4	48.3	39.04-57.56	77.7	0.004
Control group	Pa CO2	4	46.56	39.94-53.18	52.8	0.096
Case group	H3CO3	3	28.52	25.3-31.74	16.4	0.302
Case group	H3CO3	3	25.68	23.83-27.53	0	0.808
Control group	FEV1*	6	49	31.32-66.67	73.7	0.002
Case group	FEV1	6	46.87	31.44-62.30	71.8	0.002
Control group	FVEF/FEV	3	72.27	52.42-92.13	98.4	0.000
Case group	FVEF/FEV	3	64.06	28.15-99.98	99.6	0.000
Case group	PEFR**	4	52.22	45.57-62.87	0	0.697
Control group	PEFR	4	46.63	34.07-59.2	0	0.892
Case group	Pa O2	4	81.37	70.2-92.54	73.7	0.010
Control group	Pa O2	4	81.07	67.75-94.39	81.1	0.001
Case group	SA O2	4	92.55	87.75-97.36	45.6	0.138
Case group	SA O2	4	91.1	86.15-96.04	71.2	0.015

*FEV= Forced expiratory volume

**PEFR=Peak expiratory flow

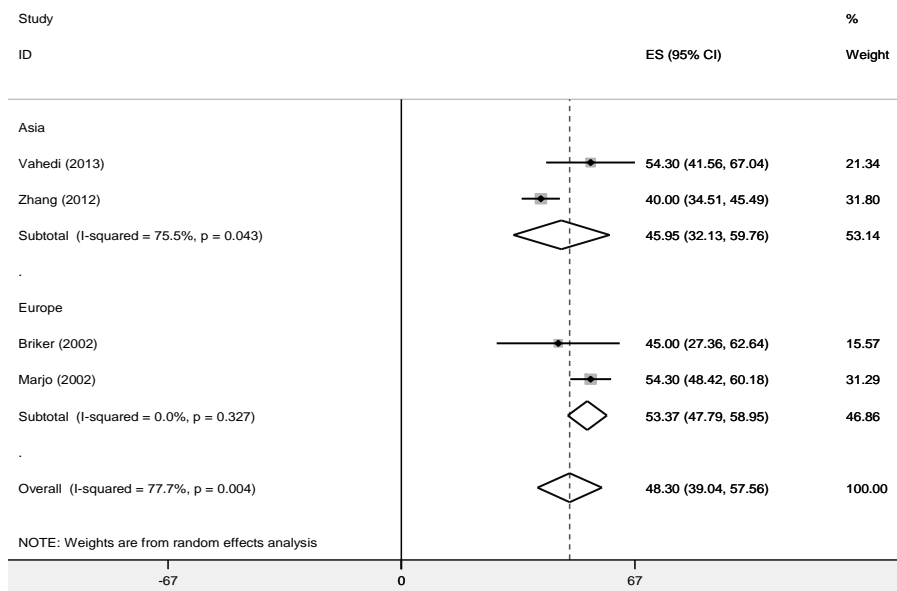


Figure 2(a). Shows the forest plot of PaCO₂ in the case group with the mean level of 48.33 (39.04-57.56).

The midpoint in each line represents the mean value in each study. The diamond shape indicates the confidence interval of the overall mean for all the studies.

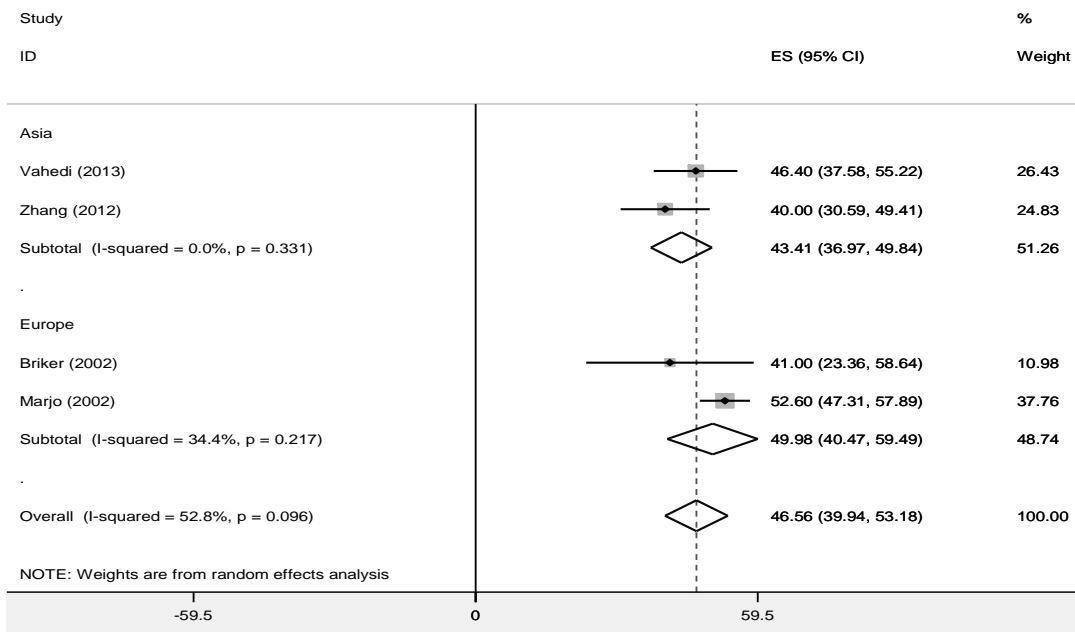


Figure 2 b). Demonstrates the forest plot of PaCo2 in the control group with the mean value of 46.56 (39.94, -53.18). The midpoint in each line represents the mean value in each study. The diamond shape indicates the confidence interval of the overall mean for all the studies.

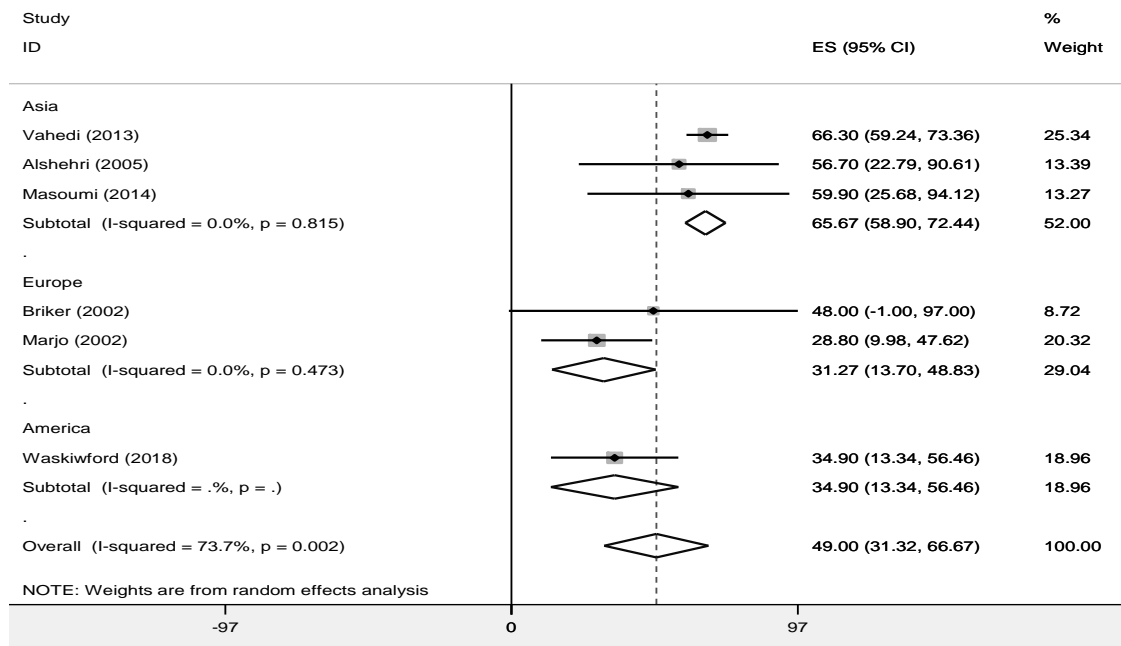


Figure 3a). The forest plot of FEV1 has been shown in the case group with the mean value as 49 (31.32-66.67). FEV= Forced expiratory volume. The midpoint in each line represents the mean value in each study. The diamond shape indicates the confidence interval of the overall mean for all the studies.

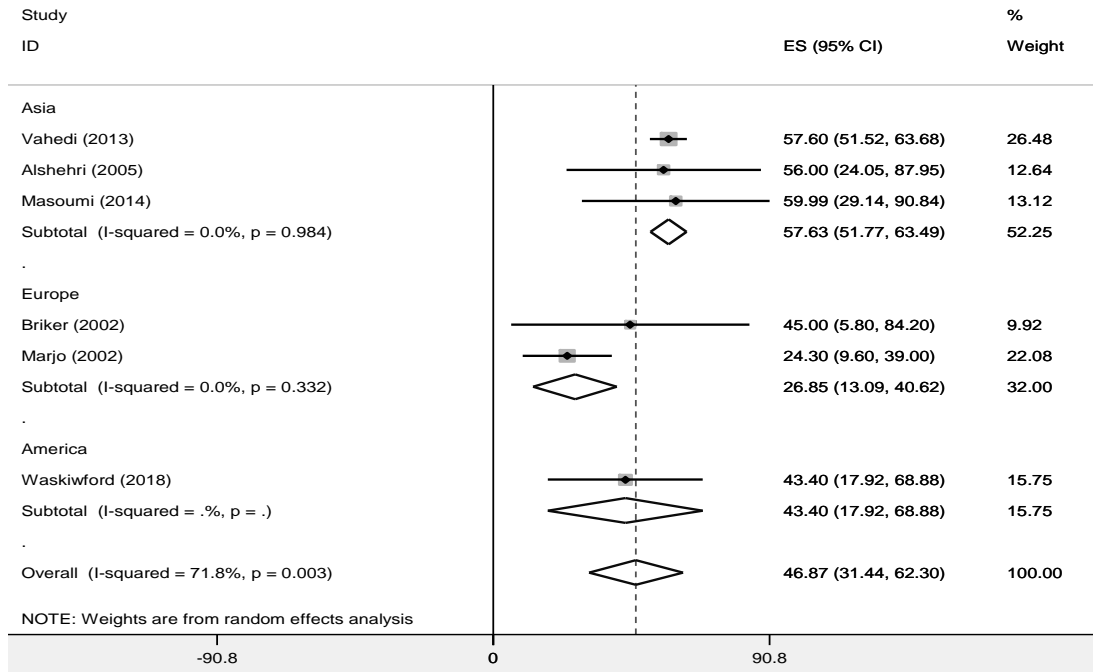


Figure 3b). Shows the forest plot of FEV1 in the control group with the mean level of 46.87 (31.44-62.30). The midpoint on each line is an estimate of the mean value in each study. The diamond shape indicates the confidence interval of the overall mean for all the studies. FEV= Forced expiratory volume

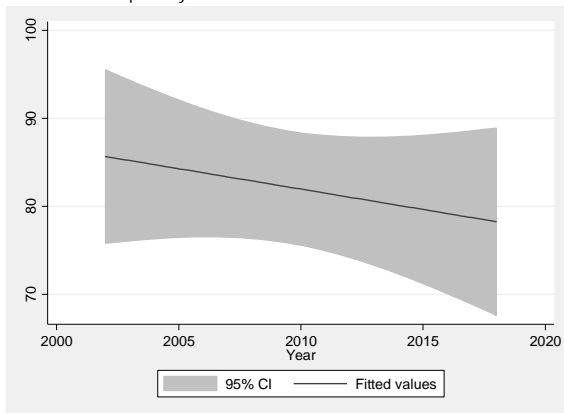


Figure 4 a). Meta-regression of heart rate based on the year of study

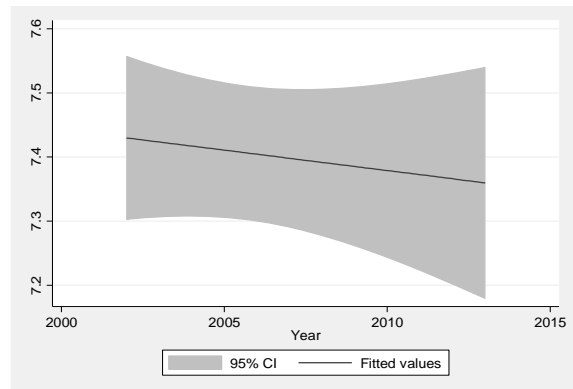


Figure 4 c). Meta-regression of pulse rate based on the year of study

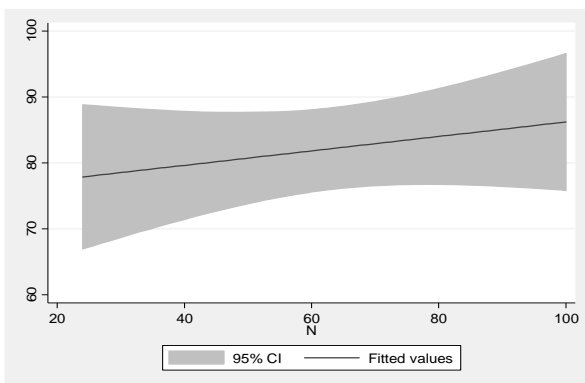


Figure 4 b). Meta-regression of heart rate based on the sample sizes

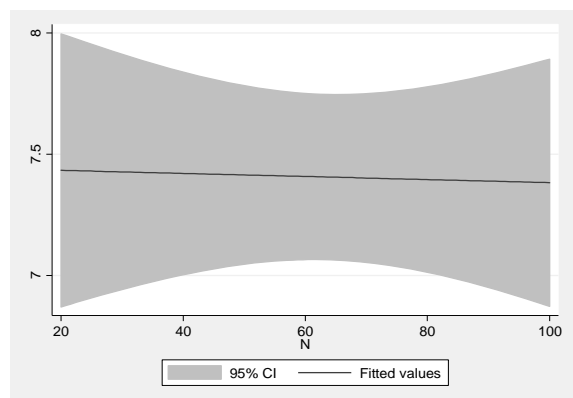


Figure 4 d). Meta-regression of pulse rates based on the sample size

DISCUSSION

This systematic review and meta-analysis of clinical trials compared the effects of nebulizing furosemide and placebo on cardiovascular and respiratory parameters in patients with COPD. Based on the results of the clinical trials investigated in the present review, nebulizing furosemide showed significant regulatory effects on respiratory rate, heart rate, blood pressure, FEV1, and PEFR; however, no significant impacts had been noticed on pH, PaCO₂, SaO₂, H₃CO₃, and PaO₂.

The results of this study showed that respiratory and heart rates were closer to the normal range in patients treated with nebulizing furosemide than those who had received a placebo indicating the efficiency of this agent on these parameters. In a clinical trial conducted by Ong et al. in 2004, it was found that the inhalation of nebulizing furosemide significantly increased bronchodilator compared with the placebo in patients with stable COPD performing exercise (20).

The results of this study showed that treatment with nebulizing furosemide improved pulse rate and blood pressure in comparison with the control group suggesting that nebulizing furosemide can be helpful in regulating cardiac and vascular functions in patients with COPD. A study by Brijker et al. revealed that discontinuation of furosemide in patients with COPD reduced PaCO₂; nonetheless, no noticeable effect was described on the oxygenation level (31).

There were no significant differences in the levels of PaCO₂, SaO₂, HCO₃, and PaO₂ comparing furosemide and placebo groups with almost the same levels in both groups. The results of this study showed that FEV1 and PEFR were closer to the reference range in COPD patients receiving furosemide than those treated with placebo. This finding suggests that furosemide can improve FEV1 and PEFR in these patients. In a clinical trial study by Sheikh Motahar Vahedi et al. on 100 patients with COPD, the administration of 40 mg furosemide significantly improved FEV1, dyspnea, pH, mean blood pressure, and heart rate (30). Likewise, a double-blind randomized clinical trial has

recently shown that furosemide inhalation at the doses of 40 and 120 mg along with physical activity had no effects on respiratory parameters in healthy men (21).

Limitations

The variables evaluated in the studies were limited. In some studies, different therapeutic duration and courses, as well as different furosemide doses had not been applied. In some studies, no comparisons had been conducted between males and females or among different age groups with merely mentioning overall alternations.

CONCLUSION

According to our results, nebulizing furosemide can improve and normalize the vital signs and other respiratory variables in patients with COPD. Also, the nebulizing furosemide has few complications and can be used according to the patient's clinical condition.

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