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The Adjunctive Effect of Nebulized Furosemide in Acute Treatment of Patients with Chronic Obstructive Pulmonary Disease Exacerbation: A Randomized Controlled Clinical Trial

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Abstract

Objective: To examine the effect of nebulized furosemide as an adjunct to the conventional treatment of patients with chronic obstructive pulmonary disease (COPD) exacerbation in an emergency department.

Method: In this randomized double-blinded clinical trial, patients with the clinical presentation of COPD exacerbation were randomized to receive 40 mg nebulized furosemide (intervention group) or placebo (control group) as an adjunct to their conventional treatments. Changes in the severity of dyspnea (dyspnea-Visual Analog Scale), Forced Expiratory Volume in one second (FEV_1), arterial blood gas (ABG) measurements, blood pressure, pulse rate and respiratory rate were assessed at the baseline and compared in the two groups, one hour after the treatment.

Result: One hundred COPD patients with the mean age of 73.1± 8.7 were randomized. Clinical parameters including the severity of dyspnea and FEV1 improved significantly after both therapies, whereas higher FEV1 and lower severity of dyspnea were observed in the furosemide group compared to the placebo group ($p<0.001$). In addition, patients treated with nebulized furosemide yielded a significant elevation in the mean pH and Pao2 an hour after the treatment ($p<0.001$). There was a significant decrease in the mean blood pressure and pulse rate in the furosemide group compared with the placebo.

Conclusion: Nebulized furosemide as an adjunctive to the conventional treatment demonstrated additional clinical benefits for acute management of patients with COPD exacerbation. This may provide an additional therapeutic option in treatment of patients with COPD exacerbation.

Keywords: COPD, dyspnea, nebulized furosemide, bronchodilation, arterial blood gas

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Introduction

Dyspnea is a common and overriding symptom of chronic obstructive pulmonary disease (COPD) that contributes to activity limitation, anxiety and poor quality of life [1-4]. In spite of prevalence and burden of dyspnea, its effective management remains a significant challenge for physicians and requires the exploration of new treatments [3, 5].Irreversible underlying changes to the lungs in patients with COPD often makes it difficult to improve dynamic ventilatory mechanic in acute dyspnea states. Therefore, in complement to the therapeutic measures that targeted the underlying causes, the care of dyspnea has shifted to improve patients' perception of dyspnea by using medications that modulate the bronchopulmonary vagal afferent activity [6-9]. Some studies showed that inhalation of furosemide, a common diuretic, alleviates dyspnea through modulating vagal afferent activity in animal lung models [10] and improves the intensity of induced dyspnea in healthy individuals. [11, 12] Further studies suggested that nebulized furosemide might be effective against dyspnea of asthma [13] and lung cancer [14, 15]. Ong, et al. and Jenson, et al. evaluated the efficacy of inhalational furosemide in COPD patient [16, 17] and supported the use of nebulized furosemide as a therapeutic approach in patients with COPD exacerbation [3, 5, 17, 18]. Studies on the use of nebulized furosemide in COPD were mainly conducted on stable patients with induced dyspnea; therefore, the short-term effect of nebulized furosemide in acute exacerbations of COPD has to be investigated. The goal of this study was to evaluate the effect of nebulized furosemide as an adjunct to the conventional therapy in acute management of patients with COPD exacerbations in an Emergency Department. We hypothesized that this combined therapeutic option would promote an improved clinical and physiological impact for the acute treatment of patients with COPD exacerbation.

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Methods

In this randomized, double-blinded, clinical trial, a convenience sample of patients was enrolled at the Emergency Department of Hazrat-e-Rasool Hospital, a tertiary medical center of Tehran University of Medical Sciences, Tehran-Iran between November 2009 and March 2010. The study was performed in accordance with the declaration of Helsinki and the subsequent revisions. The study was approved by the Institutional Review Board of our university. All participants or their next-of-kin provided a written informed consent before being included in the study. Both patients and physicians who administered the interventions were blinded to the medications. The inclusion criteria were COPD patients with the presentation of dyspnea exacerbation, who were older than 18 years, and were clinically stable with no need for positive pressure ventilation. COPD was defined according to the standards of the American Thoracic Society and COPD GOLG guideline [1, 19], in which worsening of dyspnea of COPD within 24-hours before hospital admission indicated dyspnea exacerbation. Patients with history of asthma, atopy, congestive heart failure and lung cancer were excluded. Ong et al. reported 42% improvement in the intervention group compared to 15% in the placebo group. We used STATA software's "sampsi" command to estimate the minimum required sample size to detect a similar difference with type I and type II errors both set at 5%. The sample size was estimated to have 78 subjects. To cope with noncompliance, 100 patients were recruited to the study. We used SPSS version 15 (SPSS 15.0, SPSS Inc., Chicago, IL) to randomize eligible patients into groups 1 (intervention group) or 2 (placebo group). An assistant, who was not involved with the patients' care, was responsible to blindly provide medications by filling 10 similar vials labeled 1 and 2 consequently with 4ml furosemide (20mg/2ml, Caspian Tamin Pharmaceutical Company, Iran) and 4 ml 0.9% saline on a daily basis. Patients in group 1 (intervention group) received vial labeled 1 (contained 40 mg furosemide) and group 2 (placebo group) received vial labeled 2 (contained 0.9% saline as placebo).

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On admission to the study, pulse rate (PR), respiratory rate (RR), mean arterial blood pressure (MaBP), forced expiratory volume in one second (FEV_1), and arterial blood gas (ABG) measurements including PH, $Paco_2$, Pao_2 and Hco_3, oxygen Saturation were determined. FEV_1 was measured by using a spirometer (Spirolab II, MIR, Italy).

In this study, we sought to determine the change in dyspnea, by measuring a visual analog scale (VAS). The tool we used consisted of a horizontal line with 10 equally spaced markers ranging from zero (no shortness of breath) to 10 (the worst shortness of breath). Shortness of breath was described as an urge to breathe. The patients were asked to point one ordinal number from zero to ten on the horizontal line of VAS to express the severity of dyspnea. ABG samples were obtained by percutaneous insulin needle puncture of palpable radial artery in breathing room air. The samples were analyzed within a maximum of 30 minutes. All patients received conventional treatment including 0.5 l/min supplemental oxygen for 30 minutes, 200µg Salbutamol spray, 40µg Ipratropium spray, and 200 mg intravenous Hydrocortisone. Salbutamol and ipratropium were taken by metered-dose inhalers (MDIs) without spacer. Along with conventional therapy, patients in group 1 received 4 ml furosemide (40 mg) and patients in group 2 received 4 ml 0.9% normal saline. Both furosemide and saline were administered by nebulizer (Omron NE-U17, Japan). All variables were measured again one hour after receiving the study medications. The primary endpoints were changes in post-treatment forced expiratory volume in one second (FEV_1) and the severity of dyspnea. Secondary end-points were changes in clinical and laboratory respiratory parameters.

The data were analyzed using SPSS software for windows (SPSS 15.0, SPSS Inc., Chicago, IL). Chi-square test was used for the analysis of categorical variables. Independent t-test was utilized to compare baseline variables between the study groups and also to specify the difference of post-treatment measurements compared to pre-treatment ($\Delta x = X_1 - X_0$). Results were reported as mean (± Standard Deviation). $p<0.05$ was considered as statistically significant.

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Results

One hundred patients with COPD exacerbation were included. The mean age of the patients was 73.1± 8.7 years and 63 were males. The mean baseline FEV_1 was 53.8%±4.4 (ranging from 44% to 63%) according to COPD GOLD guidelines. Baseline characteristics of the study groups are shown in table 1. There was no statistically significant difference between the two groups with regard to pre-treatment clinical variables except for bicarbonate level and pulse rate (see table 1).

For the primary endpoints, a decline in the severity of dyspnea, and an increase in FEV1 were observed in both groups; however, the improvement was more noticeable in the intervention group (P<0.001, Table 2). While Respiratory rate decreased; PH and PaO2 increased after treatment and the improvement was more significant in the intervention group (table 2). Patients presented with a lower FEV1 on admission had gained more benefits from furosemide compared to those with higher baseline FEV1 (Figure 1). The mean arterial blood pressure and pulse rate decreased in the intervention group while they slightly increased in the placebo group and the difference was statistically significant (table 2). PCO2 decreased after the treatment in both groups; however, the decrease was more noticeable in the placebo group (P<0.001, Table 2). Oxygen saturation increased in both groups and the difference between the two groups was not statistically significant.

Discussion

In this study, we evaluated the effect of adding nebulized furosemide to the conventional treatment in patients with acute COPD exacerbation in Emergency Department. The results of this study indicate that the administration of nebulized furosemide is associated with an improvement in dyspnea and physiological respiratory parameters in patients with acute COPD exacerbation. The intervention group who received nebulized furosemide experienced an improvement in the severity of dyspnea (VAS score) and a reduction in the respiratory rate that were respectively 1 scale and 4

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breaths/min more than the improvement observed in the placebo group. This difference seems clinically significant, considering the baseline values and the range of variations (table1 and table2). By “clinically significant”, we mean a change that is of clinical importance. This refers to the magnitude of a given change, while “statistical significance” indicates that a given change is unlikely to be due to change or random error. Therefore, a change may be statistically significant but clinically unimportant. Severity of dyspnea was measured according to the patients' perception. It could be expected that any improvement reported by the patients, should be clinically significant to be considered as an improvement at all.

The patients also manifested an increase in FEV_1 following the administration of nebulized furosemide compared to the placebo group that was about 7%. This change is similar to Ong et al. study that was about five percent[16]. FEV1 measurements are highly predictive of clinical outcomes during exacerbations of COPD. In a study by Denis et al. , they demonstrated that relatively small differences in FEV1 have a substantial impact on the clinical outcome [20]. Among patients who received nebulized furosemide, those with lower baseline FEV_1 experienced more improvements in the severity of dyspnea (fig 1). Since patients with lower FEV_1 are less able to bronchodilate, this improvement might be also attributed to the effect of nebulized furosemide on symptomatic relief of dyspnea that is independent of bronchodilation mechanism [3, 12].

The effects of β_2-agonists and corticosteroids on gas exchange have been previously described in COPD patients [21-23]. In this study, we sought to determine how arterial blood gas values would change when nebulized furosemide is added to the conventional therapy. The combination of O2, β_2-adrenoceptor agonist, anticholinergic and corticosteroid with an added nebulized furosemide significantly increased PH and PaO2 more than the placebo combination; however, these improvements do not seem to be clinically significant .The mean change of PaO2 contributed to furosemide was about 4mmHg and for PH, it was approximately 0.03. These findings can be attributed to a reduction in RR, an improved ventilation and increased dynamic inspiratory capacity (as was proposed in a study by Jensen et al) [17]. The administration of β-adrenergic agents is

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associated with a transient decline in PaO2 as a result of their pulmonary vasodilator effects. While severe COPD patients have a limited ability to sustain a bronchodilation, increasing blood flow to poorly ventilated lung regions causes a ventilation–perfusion mismatch [21, 22, 24]. The administration of nebulized furosemide may reverse this pathological process by improving ventilation, particularly in patients who require higher doses of β_2-adrenoceptor agonists. In this study, PaCO2 decreased more in the placebo group that would argue against the hypothetical benefits of furosemide. Patients in the intervention group had higher baseline PaCO2 and bicarbonate compared to the placebo; and this may indicate a more severe and prolonged exacerbation in this group. These patients may require more time to compensate and decrease PaCO2 in spite of more significant improvements in the respiratory rate. Contrary to the findings in a study by Jenson et al., they reported that furosemide had no effect on pulmonary gas exchange [17], although in Jenson's study the study population was included. Stable COPD patients with an induced dyspnea, as opposed to COPD patients with an acute exacerbation, were presented to the emergency department in our study. Since acute exacerbation is often associated with hypoxia, hypercarbia and acidosis, it is expected that these patients show physiologically different responses.

In this study, the mean bicarbonate level decreased in conventional therapy but increased in combination therapy with furosemide .The mean rise related to furosemide was about 4 mmol/L. Considering the mean bicarbonate baseline level and its range of variation, this change could be considered clinically significant. Consistent with its expected pharmacodynamic characteristics, systemic furosemide is capable of inducing a metabolic alkalosis by increasing urinary hydrogen (H^+) loss [25]. Although the effect of nebulized furosemide on dyspnea is likely to be independent of its systemic diuretic effect [18, 26], the systemic effect of nebulized furosemide has not been ruled out [17]. Both Pulse rate and blood pressure decreased in the furosemide group respectively about 4 beats/min and 9 mmHg that is consistent with the results in the study of Rodriguez Vazquez et al. [13]; however, these changes were not clinically significant. The change in heart rate and blood pressure could explain functional cardiac effects related to this medication; however, considering multiple

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contributing factors including patients' anxiety and potential diuretic effects of furosemide,it may preclude a direct correlation between these findings.

Limitations

It is difficult to study COPD patients in an exacerbation with a controlled manner. In this study, patients in the intervention group had higher baseline bicarbonate and PaCO2 and lower paO2; furthermore, baseline severity of dyspnea was higher compared to the placebo. This may indicate more severe exacerbation in the intervention group. On the other hand, baseline FEV_1 was higher in the intervention group. All these may indicate that patients in the intervention group had milder COPD but more sever exacerbation. It might be argued that furosemide inhalators had more capability to decrease dyspnea due to higher baseline FEV_1 but the result showed that furosemide inhalators with lower FEV_1 had more significant improvement in severity of dyspnea in comparison to those with higher FEV_1 (fig 1). We did not assess the diuretic effect of nebulized furosemide and the possible systemic effect of nebulized furosemide could not be confirmed in this study.

Conclusions

The study revealed that the combination of nebulized furosemide with conventional therapy is associated with an improvement in the severity of dyspnea and physiological respiratory parameters in patients with acute COPD exacerbation. This may provide an additional therapeutic option in treatment of patients with COPD exacerbation. The possible systemic effects of nebulized furosemide should be considered in future investigations.

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References:

1. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007;176(6):532-555.

2. Fromer L, Cooper CB. A review of the GOLD guidelines for the diagnosis and treatment of patients with COPD. Int J Clin Pract 2008;62(8):1219-1236.

3. Ora J, Jensen D, O'Donnell DE. Exertional dyspnea in chronic obstructive pulmonary disease: mechanisms and treatment approaches. Curr Opin Pulm Med 2010;16(2):144-149.

4. Seamark DA, Seamark CJ, Halpin DM. Palliative care in chronic obstructive pulmonary disease: a review for clinicians. J R Soc Med 2007;100(5):225-233.

5. Horton R, Rocker G. Contemporary issues in refractory dyspnoea in advanced chronic obstructive pulmonary disease. Curr Opin Support Palliat Care 2010;4(2):56-62.

6. Undem BJ, Kollarik M. The role of vagal afferent nerves in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005;2(4):355-360; discussion 371-352.

7. Uronis HE, Currow DC, Abernethy AP. Palliative management of refractory dyspnea in COPD. Int J Chron Obstruct Pulmon Dis 2006;1(3):289-304.

8. Nishino T. Dyspnoea: underlying mechanisms and treatment. Br J Anaesth 2011;106(4):463-474.

9. Kallet RH. The role of inhaled opioids and furosemide for the treatment of dyspnea. Respir Care 2007;52(7):900-910.

10. Sudo T, Hayashi F, Nishino T. Responses of tracheobronchial receptors to inhaled furosemide in anesthetized rats. Am J Respir Crit Care Med 2000;162(3 Pt 1):971-975.

11. Moosavi SH, Binks AP, Lansing RW, Topulos GP, Banzett RB, Schwartzstein RM. Effect of inhaled furosemide on air hunger induced in healthy humans. Respir Physiol Neurobiol 2007;156(1):1-8.

12. Nishino T, Ide T, Sudo T, Sato J. Inhaled furosemide greatly alleviates the sensation of experimentally induced dyspnea. Am J Respir Crit Care Med 2000;161(6):1963-1967.

13. Rodriguez Vazquez JC, Pino Alfonso PP, Gassiot Nuno C, Paez Prats I, Fernandez Manzano E. Assessment of the bronchodilator effect of inhaled furosemide compared to salbutamol in asthmatic patients. J Investig Allergol Clin Immunol 1998;8(2):115-118.

14. Shimoyama N, Shimoyama M. Nebulized furosemide as a novel treatment for dyspnea in terminal cancer patients. J Pain Symptom Manage 2002;23(1):73-76.

15. Kohara H, Ueoka H, Aoe K, Maeda T, Takeyama H, Saito R, et al. Effect of nebulized furosemide in terminally ill cancer patients with dyspnea. J Pain Symptom Manage 2003;26(4):962-967.

16. Ong KC, Kor AC, Chong WF, Earnest A, Wang YT. Effects of inhaled furosemide on exertional dyspnea in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;169(9):1028-1033.

17. Jensen D, Amjadi K, Harris-McAllister V, Webb KA, O'Donnell DE. Mechanisms of dyspnoea relief and improved exercise endurance after furosemide inhalation in COPD. Thorax 2008;63(7):606-613.

18. Currow DC, Ward AM, Abernethy AP. Advances in the pharmacological management of breathlessness. Curr Opin Support Palliat Care 2009;3(2):103-106.

19. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. Am J Respir Crit Care Med 1995;152(5 Pt 2):S77-121.

20. Niewoehner DE, Collins D, Erbland ML. Relation of FEV(1) to clinical outcomes during exacerbation of chronoc obstractive pulmonary diesease. Department of Veterans Affairs Cooperative Study Group. Am J Respir Crit Care Med 2000;161(4 pt 1):1201–1205.

21. Khoukaz G, Gross NJ. Effects of salmeterol on arterial blood gases in patients with stable chronic obstructive pulmonary disease. Comparison with albuterol and ipratropium. Am J Respir Crit Care Med 1999;160(3):1028-1030.

22. Whale CI, Sovani MP, Mortimer K, Oborne J, Cooper S, Harrison TW, et al. Effects of rac-albuterol on arterial blood gases in patients with stable hypercapnic chronic obstructive pulmonary disease. Br J Clin Pharmacol 2006;62(2):153-157.

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23. Ando F, Ruggeri P, Girbino G, Cazzola M. Tiotropium and salmeterol/fluticasone combination do not cause oxygen desaturation in COPD. Respir Med 2008;102(6):815-818.

24. Stephenson A, Seitz D, Bell CM, Gruneir A, Gershon AS, Austin PC, et al. Inhaled anticholinergic drug therapy and the risk of acute urinary retention in chronic obstructive pulmonary disease: a population-based study. Arch Intern Med 2011;171(10):914-920.

25. Brijker F, Heijdra YF, van den Elshout FJ, Folgering HT. Discontinuation of furosemide decreases PaCO(2) in patients with COPD. Chest 2002;121(2):377-382.

26. Minowa Y, Ide T, Nishino T. Effects of inhaled furosemide on CO(2) ventilatory responsiveness in humans. Pulm Pharmacol Ther 2002;15(4):363-368.

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Figure 1 legend:

Figure1. Improvement in dyspnea, following treatment with nebulized furosemide vs. placebo, according to FEV_1 at admission (Salin= Saline solution, Furosmide = Nebulized Furosemide, FEV1 = Forced expiratory volume in one second).

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Table1. Baseline characteristics of patients in study groups

	Study groups				P Value
	Intervention (N=50)		Placebo (N=50)		
	Mean	SD	Mean	SD	
Age (year)	73.2	8.6	73.0	9.0	0.93
Respiratory rate (breaths/min)	26.4	6.3	27.3	2.6	0.39
MaBP (mmHg)	108.4	16.9	105.4	11.9	0.31
Heart rate (beats/min)	88.9	17.5	101.0	10.9	<0.001
PH	7.29	0.06	7.27	0.06	0.08
paCO2 (mmHg)	55.6	12.8	51.8	6.8	0.07
paO2 (mmHg)	73.2	11.3	76.7	6.7	0.06
Hco2(mmol/L)	31.6	6.0	28.7	2.5	<0.01
O_2Sat (%)	84.8	9.6	82.8	4.7	0.18
FEV1 (%)	54.8	3.9	52.7	4.6	0.02
Severity of dyspnea (VAS)	5.6	0.9	5.4	0.7	0.26

SD: Standard deviation; MaBP: mean arterial blood pressure; O_2Sat: oxygen saturation measured by Arterial Blood Gas; FEV_1: forced expiratory volume in 1 second; VAS: visual analog scale.

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Table2. Comparison of change in clinical and laboratory respiratory parameters after treatment

Parameters	Study groups				P Value
	Intervention		Placebo		
	Mean	SD	Mean	SD	
Respiratory rate (breaths/min)	-7.0	3.2	-3.3	2.1	< 0.001
MaBP (mmHg)	-8.9	10.4	0.6	7.3	< 0.001
Heart rate (beats/min)	-4.9	11.9	0.4	6.8	0.007
PH	0.07	0.03	0.04	0.02	< 0.001
PaCO2 (mmHg)	-1.3	6.5	-5.4	4.5	< 0.001
PaO2 (mmHg)	12.6	5.2	8.2	4.9	< 0.001
Hco2 (mmol/L)	1.9	3.8	-2.2	1.6	< 0.001
O_2Sat (%)	7.4	7.4	6.7	2.7	0.54
FEV_1 (%)	11.5	3.6	4.9	3.1	< 0.001
Severity of dyspnea (VAS)	-2.7	1.0	-1.6	0.8	< 0.001

SD: Standard deviation; MaBP: mean arterial blood pressure; O_2Sat: oxygen saturation measured by Arterial Blood Gas; FEV_1: forced expiratory volume in one second; VAS; visual analog scale.

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