NONOPIOID THERAPY FOR CANCER RELATED DYSPNEA PALLIATION IN THE ED: A RANDOMIZED DOUBLE BLIND CLINICAL TRIAL

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ABSTRACT

Introduction*: Dyspnea is a frequent and devastating symptom among patients with cancer, and is a prognostic indicator of survival. The management of cancer-related dyspnea remains a challenge due to lacking systematic guidelines for clinical care. The mainstay of cancer related dyspnea palliation is being considered altering central perception, and morphine is still the first choice of therapy. Conventional management of cancer related dyspnea might not be suitable for emergency department. Palliative treatment of a cancer patient shouldn't always be planned as end of live care in the ED. There has been no study published that describes the efficacy of bronchodilators or respiratory muscle relaxants inpatients experiencing dyspnea with lung cancer.*

The aim of the study was to determine effect of salbutamol, beta 2 agonist and magnesium sulfate, respiratory muscle relaxants for improvement on respiratory capacity in patients with lung cancer.

Methods*: This was a randomized, double blind clinical trial. Adult patients with lung cancer, with a Peak Expiratory Flow Rate (PEFR) of <250 L/min, who did not receive bronchodilators and not requiring assisted ventilation were included. Patients were randomized to receive either serial three doses of 2.5 mg salbutamol plus 1500 mg magnesium sulfate in IV 100 mL 0.9% NaCl or serial three doses of 2.5 mg salbutamol plus 100 mL IV 0.9% NaCl. We defined the primary outcome measures as the changes in PEFR and Fischl index over time (at 0 and 120 min).*

Results*: Salbutamol therapy increased mean PEFR from 127.4 liters/minute to 169.4 liters/minute (p<0.01), while salbutamol plus magnesium therapy increased it from 131.1 to 174.9 liters/minute (p<0.01). Both therapies resulted in improvement in Fischl Scores. After treatment PEFR and Fischl Scores were similar between the two groups (p=0.74, p=0.19).*

Conclusion*: Optimal management of dyspnea in cancer patients requires an understanding of the causes and decision-making process must consider of the patient's general condition, the presence and severity of symptoms. The results of this study revealed, salbutamol, a non-opioid, beta 2-agonist agent, provided significant improvement on respiratory capacity in patients with cancer related dyspnea. However, adding IV Magnesium therapy to nebulized salbutamol has no beneficial effect.*

Keywords*: dyspnea, cancer, and emergency department.*

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Introduction

Dyspnea is a frequent and devastating symptom among patients with advanced cancer, and is a prognostic indicator of survival[1]. Dyspnea precipitates physical and psychological distress, severely impedes patients' quality of life, and is associated with anxiety and depression[2,3]. In contrast to pain, the mechanism of cancer-related dyspnea is less understood. There are many causes of dyspnea in patients with cancer. Dyspnea can be a direct effect of the cancer or an effect of therapy. In addition to cancer, patients may have chronic obstructive pulmonary disease, congestive heart failure, pleural effusion, pneumonia, or airflow obstruction[4].

The incidence of lung cancer in Chronic Obstructive Pulmonary Disease (COPD) patients is 16.7 cases per 1000 person years, and may be high-

er than previously reported[5,6]. Successful dyspnea management in patients with COPD might be applied to the management of dyspnea in patients with lung cancer because of the similarity of some causes and complications in the two diseases[7].

Dyspnea may also be a clinical expression of the syndrome of overwhelming cachexia (present in 80% of patients with advanced cancer) and asthenia (present in 90% of patients with advanced cancer) even in the absence of lung or heart disease[8]. In some patients with advanced cancer, dyspnea may be a clinical manifestation of cachexia and asthenia. Although it is possible that in some patients with advanced cancer, magnesium may reduce dyspnea as a smooth muscle relaxant and a bronchodilator.

Opioids have been used to treat dyspnea from various causes for more than a century. In a meta-analysis of studies that evaluated opioids in treating breathlessness from various etiologies, a statistically significant positive effect on the sensation of breathlessness was found[2]. Nevertheless, as we found in the Currow, et al trial 38% of patients unfortunately do not respond to opioids for dyspnea[9]. We as clinician also have to balance the risks of opioid therapy, in daily clinical practice, opioids are not widely used for cancer-related dyspnea in terminally ill patients with cancer, and few RCTs have appraised the role of opioids in this population.

Appropriate dyspnea palliation provides numerous benefits in the emergency department: improved outcomes, reduced hospital length of stay, improved patient and family satisfaction, less utilization of intensive care and cost savings[10]. Many studies regarding interventions to alleviate dyspnea of cancer have investigated opioids, oxygen, psychotropic drugs, and nebulized furosemide[1,2,11-13]. Managing cancer-related dyspnea in the Emergency Department (ED) remains a challenge due to the lack of systematic guidelines for clinical care. It is a common practice in the ED to use short-acting nebulized bronchodilators (Ipratropium bromide and salbutamol) for dyspnea whether or not it is related to cancer[14]. Although most patients are ex-or current smokers, and are at high risk for co-existing pulmonary and cardiac diseases, little is known regarding bronchodilator efficacy in cancer-related dyspnea. However, to the best of our knowledge, no study has been reported the effect of bronchodilators in patients experiencing dyspnea with cancer.

This study was conducted to evaluate effect of non-opioid agents, salbutamol versus salbutamol plus intravenous magnesium for respiratory capacity improvement in patients with lung cancer.

Materials and methods

Study design and setting

This prospective, randomized, double blind clinical study was conducted in an academic tertiary hospital, which has approximately 40,000 ED admissions per year, over a 1-year period. The institutional ethics committee approved the study. Informed consent was obtained from all patients before enrollment into the study. The study was conducted at an ED staffed by investigator. Participants will be randomized using computer-generated random table (1:1 randomization) by responsible investigator. Allocation concealment will be ensured, as the central randomization code will not release until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed. The senior residents who performed patients' care and collected the data were blinded treatment arms. The emergency room nurse performed treatments according to assigned randomization number. Responsible investigator was assessed the outcomes

Study population

Patients presenting to the ED with lung cancer and dyspnea were enrolled in the study. Patients were eligible for recruitment if they satisfied the following inclusion criteria: adults 18 to 65 years of age; presentation to the ED with the complaint of shortness of breath and, such as dyspnea on exertion, wheezing, and accessory muscle use; not requiring assisted ventilation, peak expiratory flow rate (PEFR) of <250 and provision of informed consent.

Patients were excluded from the study if any of the following factors were present: known hypersensitivity to salbutamol or magnesium; dysrhythmias, angina; known history of renal insufficiency (creatinine clearance <50 mL/min); receipt of theophylline product, beta 2 agonist or an anticholinergic agent within 6 hours of arrival to the ED; or refusal to participate in the study.

Intervention

Upon admission to the ED, all patients underwent a standard history and physical examination, including assessment of vital signs (blood pressure, pulse rate, respiratory rate, and temperature).

Each patient was monitored by means of pulse oximetry. Immediately before receiving the study drug, pulmonary function measures (PEFR) were determined by using the Mini Wright Standard Peak Flow Meter Standard EN 23747; Clament Clarke, Inc., Solmed, UK) for eligibility. The best of 3 acceptable maneuvers was used to assess the patients' pulmonary function at each time point.

Serum magnesium levels were not obtained in the study.

Patients were randomized to receive either a series of three doses of 2.5 mL (2.5 mg) salbutamol solution plus 10 mL (15% solution, 1500 mg) Magnesium solution in IV 100 mL 0.9% NaCl or a series of three doses of 2.5 mL (2.5 mg) salbutamol solution plus 100 mL IV 0.9% NaCl. Patients were monitored for occurrences of potential adverse drug reactions, including but not limited to skin flushing, nausea, vomiting, sedation, somnolence, hypotension, dizziness, light-headedness, and taste abnormalities.

Assessment

Our study focuses on dyspnea reduction bet dyspnea is a subjective phenomenon. We did not prefer subjective measure on dyspnea reduction. Rather than we prefer objective measure of respiratory capacity improvement. So we defined the primary outcome measures as the changes in the PEFR and Fischl index over time (at 0 and 120 min).

PEFR is a person's maximum speed of expiration, as measured with a peak flow meter, a small, hand-held device used to monitor a person's ability to breathe out air. It measures the airflow through the bronchi and thus the degree of obstruction in the airways[15]. Although not validated as many of other scales, the Fischl index was used as clinical assessment tool in addition to PEFR in this study. The Fischl index is composed of seven objective clinical variables assigning one point for each. It takes into account dyspnea, accessory muscle use, wheeze, pulse rate of >120/min, respiratory rate of > 30/min, pulsus paradoxus of > 18 mmHg, and a PEFR of <120 L/min. An index of 3 or lower was associated with adequate response to treatment according to the original article[16]. All 7 of the clinical criteria had interrater reliability (k) values greater than 0.6.

Statistical analysis

The study data were recorded and analyzed using Statistical Package for Social Sciences (SPSS) for Windows version 16.0. (SPSS Inc., Chicago, IL, USA). In order to estimate the required sample size, a 15% or greater difference in the mean PEFR improvement between the first assessment and salbutamol treatment and a 15% or greater difference in the mean PEFR improvement between two treatment groups was considered to be clinically significant because this value is traditionally used as the threshold for bronchodilator induced reversibility of dyspnea (17). Sample size calculation was carried out using the G power program with an assumption of p1: 0.85, p2: 0.70, α: 0.05 and β: 0.80 was used. The requisite sample size was calculated as 212 (18). Visual (histogram) and analytical (the Kolmogorov-Smirnov test) methods were used to assess the normal distribution of the variables. Qualitative variables were expressed as frequencies and percentages, and quantitative variables were provided as means or medians, depending on their normal distribution, together with 95% confidence intervals (CIs). The Wilcoxon signed-rank test was used for intragroup comparisons, and the Kruskal-Wallis one-way analysis of variance or Wilcoxon rank-sum test was used for intergroup comparisons.

Results

Patient flow during the study period is shown in Figure 1. Of the 91 patients included, 45 (49.5%) were female, and the mean age was 54.7 (95% CI: 51.8-57.7).

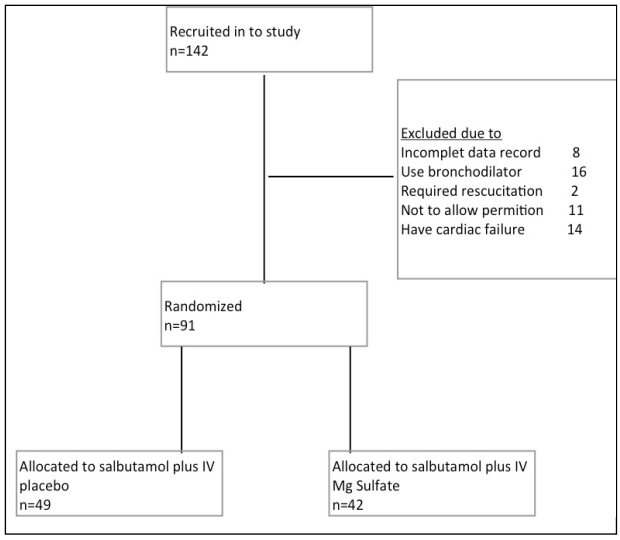

Fig. 1: Patient flow during the study period.

Forty-nine (53.8%) of the patients were allocated to receive nebulized salbutamol, and 42 (46.2%) to nebulized salbutamol plus intravenous

Magnesium. Baseline characteristics and main causes of dyspnea were similar between the groups (Table 1). Fifty-two (57.1%) patients had COPD and 30 (32.9%) had bronchospasm. Nineteen patients with bronchospasm had COPD. Main causes of dyspnea were pleural effusion, pain, bronchospasm, and pneumonia. The causes of dyspnea were not found in eleven patients.

	Salbutamol+placebo	Salbutamol+MgSO4	P Value
Characteristics			
Age m, 95%CI	53.6 (50.8-56.6)	(52.5-58.7)	0.23
Sex (F) n,%	21 (23)	24 (26.3)	0.79
Complaint			
Dyspnea n, %	49 (100)	42 (100)	
Accessory muscle use n, %	26 (53)	21 (50)	0,60
Wheeze n, %	16 (32.6)	18 (42.8)	0.2
Vital Sign			
PR /min, SD+/-	108 (11)	113 (9)	0.46
RR /min, SD+/-	32 (7)	29(5)	0.58
SBP (mmHg), m, SD+/-	148 (17)	132 (14)	0.69
DBP (mmHg), m, SD+/-	92 (11)	98 (17)	0.21
Fever (C), m, SD+/-	36.4 (0.7)	36.8 (0.5)	0.82
Saturation (%), m, SD+/-	84 (15)	87 (9)	0.47
Main Causes of Dyspnea			
Lung Cancer n, %	14 (15.4)	11 (12.1)	0.63
Bronchospasm n, %	13 (14.2)	17 (18.7)	0.59
Pleural Effusion n, %	3 (3.3)	2 (2.2)	0.79
Pneumonia n, %	9 (9.9)	8 (8.8)	0.89
Unknown n, %	8 (8.8)	6 (6.6)	0.67
Cachexia	8 (8.8)	9 (9.9)	0.67

Table 1: Baseline characteristics, vital sign, and main causes of dyspnea in salbutamol + placebo (n = 49) and salbutamol + $MgSO_4$ (n = 42) patients with cancer related dyspnea presenting to our emergency department.
PR: Pulse Rate, RR: Respiratory Rate, SBP: Systolic Blood Pressure, Diastolic Blood Pressure CI: Confidence Interval, n: Noun, m: Mean, SD: Standard deviation, MgSO4: Magnesium Sulfate

Main Result

Initial measurements of PEFR and Fischl scores change over time are illustrated in Figure 2. The baseline PEFR and Fischl scores were similar in both groups (p=0.77, p=0.53, respectively). Salbutamol therapy increased the mean PEFR from 127.4 L/min (95% CI: 115.8-138.8) to 169.4 L/min (95% CI: 155.3-183.7) (p<0.01), while salbutamol plus magnesium therapy increased the mean PEFR from 131.1 L/min (95% CI: 116.9-145.2) to 169.4 L/min (95%CI: 155.3-183.7) (p<0.01).

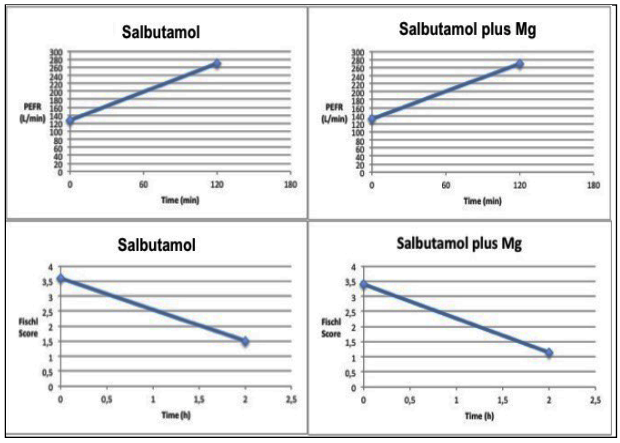

Fig. 2: In both treatment groups the mean PEFR increased with time and the mean Fischl score decreased over time.

Both therapies resulted in improved Fischl scores. The mean Fischl scores decreased from 3.6 (95% CI: 3.3-3.9) to 1.51 (95% CI: 1.21-1.81) with salbutamol therapy (p<0.01). The mean Fischl scores decreased from 3.4 (95% CI: 3.0-3.8) to 1.14 (95% CI: 1.1-1.18) with salbutamol plus magnesium therapy (p<0.01). After treatment, the PEFR and Fischl scores were similar between the two groups (p=0.74, p=0.19 respectively) (Table 2).

	Salbutamol+placebo	Salbutamol+MgSO4	P Value
PEFR L/min			
Baseline (m, 95% CI)	127.4 (115.3-183.7)	131.1 (116.9-145.2)	0.77
Final (m, 95% CI)	269.1 (255.3-283.7)	269.4(255.6-284.2)	0.74
P Value	<0.01	<0.01	
Increased in PEFR	141.7	138.3	
Fischl Index			
Baseline (M, IQR)	3.6 (3.3-3.9)	3.4 (3.0-3.8)	0.53
Final (M,IQR)	1.51 (1.2-1.8)	1.14 (1.0-1.3)	0.19
P Value	<0.01	<0.01	
Improvement in Fischl Score	2.09	2.26	

Table 2: The increase in mean PEFR and the decrease in mean Fischl Score revealed, both therapies provided significant improvement on respiratory capacity in patients with cancer related dyspnea.
PEFR: Peak Expiratory Flow Rate, L/min: Liter per minutes, m: mean, M:median, CI: Confidence Intervale, IQR: Interquarter range, Mg: magnesium

We found that baseline dyspnea decreased in 84 patients (92%) with either nebulized salbutamol or salbutamol plus magnesium and that the response was sustained over several hours. These patients were discharged from the ED with the long-acting beta agonists and follow up instructions. Seven patients had pneumonia with lung cancer admitted the hospital due to ongoing respiratory distress. No patient applied to the emergency department again in subsequent week. No adverse events were observed in the groups.

Discussion

The results of this study revealed, salbutamol, a non-opioid agent, provided significant improvement on respiratory capacity in patients with cancer related dyspnea. However, intravenous magnesium in combination with salbutamol did not provide any benefit in addition to that provided by salbutamol alone.

Currently, the mainstay of dyspnea palliation is changing central perception of dyspnea, and morphine is still the first choice of pharmacological therapy[19-24]. Opioids are in use for the treatment of shortness of breath since the end of the 19th century. However, the use of opioids decreased significantly with a finding that associated with respiratory depression[22].

In the 1980s, peripheral opioid receptors were discovered and direct pulmonary-targeted inhaled opioids with less side-effects was thought to be used in the treatment of dyspnea[25].

Higher-level clinical evidence consistently shows that inhaled opioids are not effective in improving dyspnea in patients with chronic cardiopulmonary diseases, including COPD and low-level clinical evidence supports inhaled opioids for palliation of dyspnea in patients with advanced cancer[26].

Nevertheless, as we found in the Currow, et al trial 38% of patients unfortunately do not respond to opioids for dyspnea[9]. We as clinicians also have to balance the risks of opioid therapy, in daily clinical practice, opioids are not widely used for cancer-related dyspnea in terminally ill patients with cancer, and few randomized controlled trials (RCTs) have appraised the role of opioids in this population.

Short-acting beta 2 agonists are first line treatments for COPD and have been used for symptomatic treatment in patients with lung cancer[19-20]. However, to the best of our knowledge, no studies regarding the effects of bronchodilators on dyspnea in patients with cancer have been conducted.

In the literature, the close association between COPD and lung cancer, independent of smoking intensity, has been reported several times. The reported prevalence of COPD in lung cancer patients varies from 8% to 50%[8, 14, 27] One percent of patients with COPD develop lung cancer each year, while only 0.2% of patients with normal pulmonary function develop lung cancer[5]. Successful dyspnea management in patients with COPD might be applied to the management of dyspnea in patients with lung cancer because of the similarity of some causes and complications in the two diseases[7].

COPD is substantially under-diagnosed and frequently misdiagnosed[28-29]. Overlooking or misdiagnosing COPD in cancer patients may also cause undertreatment.

Since COPD and lung cancer have similar causative mechanisms such as reduction of airflow and gas exchanges due to airway obstruction and destruction of the lung parenchyma, successful management of dyspnea in patients with COPD may be applied to manage dyspnea in patients with lung cancer[30-32]. Congleton et al. found that 49% of their lung cancer patients presented with airflow obstruction. Among those, 69% had moderate or severe dyspnea[31]. Considering the evidence of airflow obstruction in many patients with lung cancer, a trial of bronchodilator therapy seems indicated.

In our study, although 52% of patients had COPD and 32.9% of patients had bronchospasm, both therapies resulted in improved Fischl scores and increased the mean PEFR. The improvement may be through the relief of bronchospasm in coexisting COPD or altering dyspnea perception through the action of pulmonary stretch receptors or the possibility of a placebo response.

Furthermore dyspnea may not relate to lung cancer alone. In a study conducted by Dudgeon et al. on 100 cancer patients with dyspnea, only half of the patients had lung cancer[33]. Dyspnea can result from different abnormalities: such as an increase in respiratory effort in order to overcome increased resistance (e.g. obstructive or restrictive lung disease, pleural effusion); an increase in the proportion of respiratory muscle required to maintain a normal workload (e.g. neuromuscular weakness, cancer cachexia); or an increase in ventilator requirements (hyperemia, hypercapnia, metabolic

acidosis, etc.). In many cancer patients different proportions of the three abnormalities may co-exist, thereby making the pathophysiological interpretation of the intensity of dyspnea more complex. Asthenia (present in 90% of patients with advanced cancer), cachexia (present in 80% of patients with advanced cancer), and severe anemia were found to be other possible causes of dyspnea in cancer patients[8].

Magnesium is the second most plentiful intracellular cation and is an essential cofactor in more than 300 different enzymatic reactions, including carbohydrate, fat, and electrolyte metabolism; nerve conduction; muscle contractility; protein synthesis; and membrane integrity[34]. The rationale for the use of magnesium in the current study is multifactorial. First, magnesium is a physiologic antagonist of calcium and therefore may relieve bronchoconstriction by decreasing the uptake and release of calcium in bronchial smooth muscle[35]. Second, magnesium has been shown to inhibit acetylcholine release from cholinergic nerve terminals, resulting in diminished excitability of muscle fiber membranes and bronchial smooth muscle relaxation[36]. Third, magnesium may directly inhibit histamine release from mast cells and may stimulate nitric oxide generation and prostacyclin synthesis[37]. Therefore, magnesium should protect the airway against bronchoconstrictor and inflammatory stimuli and provide therapeutic benefit. Furthermore, in the general population, low dietary intake of magnesium is associated with impairment of forced expiratory volume in 1 second (FEV1) and a higher risk of wheezing and airway hyperreactivity[38].

The failure of combination of magnesium and salbutamol to show any statistically or clinically significant benefit in addition to that provided by the treatment with salbutamol may be explained by several factors. Physiological beta stimulation may be involved in the regulation of magnesium status namely by homeostatic increase of magnesemia during magnesium deficiency. But conversely excessive beta stimulation namely by use of pharmacological high doses of beta-mimetics may induce a decrease of magnesemia, so, we may have not provinces the optimal dose of beta-mimetics magnesium combination. Furthermore any chronic disease like cancer may induce magnesium depletion related to a dysregulation of the control mechanisms of magnesium status.

In our study, although 17.8% of patients had cachexia, we did not obtain serum magnesium measurements. Although to obtain serum magnesium levels measurements would be reasonable to facilitate interpreting our results, intracellular magnesium content reflects its homeostasis better than serum concentration. The serum ion concentration is usually correlated with total body content, but its normal serum concentration does not always reflect the body's magnesium real stores accurately. Serum magnesium measurements might not reflect the concentrations of the cellular level exactly[39]. Furthermore, this approach appeared to prolong the time to administer the study drugs in ED setting.

Limitations

Our study had several limitations. The first limitation of this study was the lack of a baseline serum magnesium levels as discussed above.

A second limitation of this study was the measurement of primary objective. We already know that objective measures may not correlate with the subjective feeling of dyspnea[40]. Our study focuses on dyspnea reduction but dyspnea is a subjective phenomenon. We did not prefer subjective measure on dyspnea reduction. Rather than we prefer objective measure of respiratory capacity improvement. So we defined the primary outcome measures as the changes in the PEFR and Fischl index over time.

PEFR was use of as a screening tool for patients' enrollment. Although FEV1 would have been the preferred spirometric screening tool, it was not practical in the ED. There was insufficient time to instruct patients on the proper use of the spirometer for quick treatment with the initial dose of salbutamol, and thus, disposable peak flowmeters were used for this purpose. The PEFR may not accurately reflect the degree of airway obstruction and may be confounded by factors such as patient fatigue and poor effort. The Fischl index was also used rather than the PEFR alone as the primary outcome measure.

There are a large variety of scales available for the assessment of dyspnea; however, most have been used in patients with chronic pulmonary disease rather than cancer. Unidimensional tools measure the sensory component or general severity of breathlessness. All unidimensional measures such as visual analogue scale are self-administered taking only a few moments to complete. Multidimensional tools assess the impact of breathlessness on various domains such as activities of daily living, emotional and mental functioning. There are approximately 30 multidimensional tools

available, none of which have been introduced as a gold standard for dyspnea assessment[41,42].

Using scales in clinical practice is much more problematic. Dyspnea is not a specific symptom generated through a common mechanism, influencing the patient's personal perception, are closely dependent upon multiple personal factors such as socio-economic status, affective-cultural components. Selecting the most appropriate scale depends on the purpose of measurement. Measurement of dyspnea tool has to be seen in context with the person's history, physical examination and diagnostic tests seems to be the best for clinical assessment especially in emergency settings. Consequently, Fischl Index was chosen in this study. Because it promises a practical, easy to use severity assessment with objective clinical variables that are suitable for repeated measures during ED stay.

Last, ours was a single-center prospective study carried out in an ED setting. Under these unique conditions, we have many confounding factors. The current research has not demonstrated therapeutic efficacy of salbutamol in cancer related dyspnea, because of this study did not compare the treatment arms with current practice (opioids) or placebo. Although, few RCTs have appraised the role of opioids in this population and it may not be suitable to consider dyspnea palliation of a cancer patient as end of life care in the ED. We were designing a superiority study but we did not have enough power in this study. But again we want to publish this study, as a feasibility study, because increasing number of patients with lung cancer needs to dyspnea palliation in emergency department and we think this results important for patients and investigators about palliative therapy in emergency medicine.

Conclusion

The management of cancer-related dyspnea remains a challenge due to lacking systematic guidelines for clinical care. Palliative treatment of a cancer patient shouldn't always be planned as end of live care in the ED. Optimal management of dyspnea in cancer patients requires an understanding of the causes and the pathophysiological mechanisms responsible of the symptom. The decision-making process must consider of the patient's general condition, the presence and severity of symptoms, the expected survival, and the site of care. The results of this study revealed a significant improvement with salbutamol, a non-opioid agent, suggesting its therapeutic efficacy in patients with cancer related dyspnea. However, adding magnesium therapy to salbutamol has no beneficial effect. Future investigations may help to establish the management of dyspnea with cancer patients.

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