Clinical Note

Nebulized Fentanyl Citrate Improves Patients' Perception of Breathing, Respiratory Rate, and Oxygen Saturation in Dyspnea

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Abstract

*Dyspnea, a subjective symptom of impaired breathing, occurs in 70% of terminally ill cancer patients. Current treatments are suboptimal and little is known about the patient's perception of effect. We tested nebulized inhaled fentanyl citrate on patient perceptions, respiratory rate, and oxygen saturation. The study was conducted using a convenience sample of 35 cancer patients on a dedicated oncology unit. We assessed patient perception (did breathing stay the same, worsen, or improve), respiratory rate, and oxygen saturation by pulse oximetry at baseline, 5 minutes, and 60 minutes. Twenty-six of 32 (81%) patients reported improvement in breathing, 3 (9%) were unsure, and 3 (9%) reported no improvement. Oxygen saturation improved from 94.6% at baseline to 96.8% at 5 minutes and 96.7% at 60 minutes (*P = *0.0069 compared to baseline). Respiratory rates improved from a baseline of 28.4/min to 25.9/min at 5 minutes and 24.1/min at 60 minutes (*P = *0.0251 compared to baseline). No side effects were observed. Inhaled nebulized fentanyl citrate significantly improved patient perception of breathing, respiratory rate, and oxygen saturation. This inexpensive and readily available treatment may offer substantial relief of end-of-life dyspnea. Randomized trials, dose, and length of effect trials are underway.* J Pain Symptom Manage 2002;23:157–160.

Key Words

Dyspnea, patient satisfaction, terminal cancer, nebulizer, fentanyl

Introduction

Dyspnea is the subjective sensation of shortness of breath.[1] People with comparable degrees of functional lung impairment may experience varying degrees of dyspnea.[2] Dudgeon and Rosenthal state "Dyspnea means difficult breathing. It is a subjective sensation that does not correlate well with functional (time-walking, stair-climbing) and physiologic (oxygen saturation, pulmonary function tests) parameters. No reproducible, validated, patient-centered measure of dyspnea in cancer patients is available; most investigators simply ask patients to rate their dyspnea on a visual analog scale. Patients and physicians may differ significantly in their rating of this symptom; until the physiology of dyspnea is better understood, the patient's as-

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sessment of his or her breathing discomfort should be paramount."[3]

Dyspnea is exceedingly common. Ruben and Mor found that 70% of 1500 cancer patients suffered dyspnea during their last four weeks of life.[4] Although dyspnea often is accompanied by impaired respiratory function and objective indicators such as tachypnea or low arterial oxygen saturation, the correlation between dyspnea and objective measures of respiratory function is imperfect. Patients may experience dyspnea despite normal objective measures of respiratory function, and patients with extensive tumor may experience no dyspnea, or profound dyspnea without tachypnea or hypoxemia.[5,6]

Cancer-specific interventions such as surgery, radiation therapy, and chemotherapy or drainage of a pleural effusion may help. Non-pharmacological interventions, such as relaxation and breathing retraining, help decrease the suffering of breathlessness.[7,8] Unfortunately, traditional bronchodilators, mucolytic agents, and anxiolytics often do not work and adrenergic agonists and theophylline may cause increased anxiety and agitation.[9] Dyspnea often persists and patients decrease their daily activities resulting in social isolation, dependence upon others, and physiological, psychological, social, and spiritual exhaustion.

Since the late 19th century, opioids have been used to relieve breathlessness in patients with asthma, pneumothorax, emphysema, and chronic obstructive pulmonary disease.[10–15] The mechanisms of opioid action are multiple and incompletely understood. Opioids reduce oxygen consumption, but the magnitude of this effect is insufficient to explain their clinical utility.

The administration of inhaled opioids administered via nebulizer is attractive due to low cost, ease of use, and ready availability.[16–22] With the exception of one randomized controlled study of nebulized morphine, all other controlled studies have found this intervention to be ineffective,[21,23–35] and there are reports of acute respiratory depression.[36] Fentanyl citrate is widely available and its lipophilic nature could allow it to be more readily absorbed, with less bronchospasm. We studied inhaled fentanyl to answer these questions: 1) Did the patient's perception of breathing improve? 2) Did the respiratory rate significantly decrease over time? and 3) Did the oxygen saturation significantly increase over time?

Methods

This study was approved by the institutional review board. A convenience sample comprised 35 patients who were admitted to a dedicated oncology unit and complained of dyspnea (i.e., shortness of breath, breathlessness, respiratory difficulty). These patients had a variety of life-limiting diseases (Table 1). There were 20 women and 15 men, with an average age of 56 years. Of the 35 patients, 34 were using oxygen.

We obtained measurements of respiratory rate and oxygen saturation by oximetry for baseline and 5 and 60 minutes following the completion of the nebulizer treatment. One hour after treatment, nurses documented patient satisfaction with this intervention (asking "Did this nebulizer improve your breathing?") and side effects.

All patients received 25 μg of fentanyl citrate with 2 ml of saline via nebulizer. All oxygen saturation machines were calibrated to ensure accuracy. A P value of 0.05 (two-tailed) was established beforehand for significance.

Results

The primary variable was whether the patient perceived breathing to be better, worse, or unchanged. Results are shown in Table 2. A total of 81% perceived their breathing as improved, 9% did not perceive improvement in breathing, and 9% were unsure. No changes in oxygen use or angle of the head of the bed were noted by nursing staff monitoring during this period. No side effects were reported by patients or reported by nursing staff.

A repeated measures analysis of variance (ANOVA) was performed. Respiratory rate and

Table 1
The Clinical Sample

Diagnosis	Number	Percent
Lung cancer	13	37
Breast cancer	7	20
Acute leukemia	2	8.6
Lymphoma	2	5.7
Renal cell cancer	2	5.7
AIDS	1	2.9
Chronic leukemia	1	2.9
Colon cancer	1	2.9
Pulmonary embolism	1	2.9
Unknown primary	1	2.9
Sarcoma	1	2.9

Table 2
Results

	Baseline	5 minutes	60 minutes
Improvement in breathing			26/32 (81%)
Unsure of improvement			3/32 (9%)
No improvement			3/32 (9%)
Oxygen saturation, %	94.6 (1.2)	96.8 (1.17)	96.7 (1.2)
		$P < 0.0017$	$P < 0.0069$[a]
Respiratory rate, breaths/minute	28.4 (1.73)	25.85 (1.71)	24.13 (1.73)
		$P < 0.0318$	$P < 0.0251$[a]

[a]Comparing both 5 and 60 minutes with baseline.

oxygen saturation (dependent variables) were analyzed against sex, age, time, and patient perception (independent variables) as factors. There was no differences appreciated within the dependent variables. The estimated means at the three time points for respiratory rate were 28.4 (standard error 1.73), 25.85 (1.71) and 24.13 (1.73), respectively. The estimated means at the three time points for oxygen saturation were 94.6 (1.2), 96.8 (1.17) and 96.7 (1.2), respectively. There were significant differences between baseline and 5 minutes for oxygen saturation ($P = 0.0017$) and respiratory rate ($P = 0.0318$). Compared with baseline, there was significant improvement in oxygen saturation ($P < 0.0069$) and respiratory rate ($P < 0.0251$) for both 5 and 60 minutes. The 5 minute and 1 hour values were not statistically significantly different for either of the outcomes. The raw data and the fitted means are shown in Table 2.

Discussion

This study evaluated the impact of fentanyl citrate on the highly subjective complaint of dyspnea. No previous research utilizing this intervention is known. Fentanyl was a safe and effective intervention, as 81% of patients reported improvement in breathing and no side effects were noted. As the effect of the inhaled fentanyl appears to work quickly, this invention may offer benefits compared to oral opioids, which take considerably longer to become effective, and intravenous inventions, which require an invasive intervention. Improvement in respiratory rate and oxygen saturation occurred within a relatively short period (5 minutes) and was sustained for at least one hour. This patient perception of improvement in breathing is extremely important, given the subjective nature of the symptom. Also of note, while oxygen saturation and respiratory rates do not always correlate with dyspnea, both improved.

There are limitations to this study. First, it was not a placebo-controlled trial. Second, the impact of nebulized saline (the carrier) is unknown. Third, the patient activity level during this evaluation was not assessed. Therefore, change in mobility may have impacted the oxygen saturation data. Finally, we do not yet know the duration of effect, or optimum dose. The patients who did not respond (9%) require further study.

Fentanyl citrate nebulizers appear to be safe and effective in treating dyspnea in individuals with life-limiting disease processes. This study demonstrated improved respiratory rates, oxygen saturation, and improved breathing with this treatment. In addition, fentanyl is relatively inexpensive (our cost is 12 cents per dose) and readily available within the United States. More research is needed to determine the optimum dose and duration of effect.

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