Original Article

Midazolam as Adjunct Therapy to Morphine in the Alleviation of Severe Dyspnea Perception in Patients with Advanced Cancer

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Abstract
The mainstay of dyspnea palliation remains altering its central perception. Morphine is the main drug and anxiolytics have a less established role. This trial assessed the role of midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in terminally ill cancer patients. One hundred and one patients with severe dyspnea were randomized to receive around-the-clock morphine (2.5 mg every 4 hours for opioid-naïve patients or a 25% increment over the daily dose for those receiving baseline opioids) with midazolam rescue doses (5 mg) in case of breakthrough dyspnea (BD) (Group Mo); around-the-clock midazolam (5 mg every 4 hours) with morphine rescues (2.5 mg) in case of BD (Group Mi); or around-the-clock morphine (2.5 mg every 4 hours for opioid-naïve patients or a 25% increment over the daily dose for those receiving baseline opioids) plus midazolam (5 mg every 4 hours) with morphine rescue doses (2.5 mg) in case of BD (Group MM). All drugs were given subcutaneously in a single-blinded way. Thirty-five patients were entered in Group Mo, 33 entered in Mi, and 33 entered in MM. At 24 hours, patients who experienced dyspnea relief were 69%, 46%, and 92% in the Mo, Mi, and MM groups, respectively (P = 0.0004 and P = 0.03 for MM vs. Mi and MM vs. Mo, respectively). At 48 hours, those with no dyspnea relief (no controlled dyspnea) were 12.5%, 26%, and 4% for the Mo, Mi, and MM groups, respectively (P = 0.04 for MM vs. Mi). During the first day, patients with BD for the groups Mo, Mi, and MM were 34.3%, 36.4%, and 21.2%, respectively (P = NS or not significant), whereas during the second day, these percentages were 38%, 38.5%, and 24%, respectively (P = NS). The data demonstrate that the beneficial effects of morphine in controlling baseline levels of dyspnea could be improved with the addition of midazolam to the treatment. J Pain Symptom Manage 2006;31:38–47.

Key Words
Dyspnea, morphine, midazolam, cancer, anxiety, breathlessness, opioids, anxiolytic

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Introduction

Dyspnea remains one of the most challenging symptoms to manage in the setting of advanced malignancy[1] and it is one of the most common symptoms in advanced cancer patients.[2] The prevalence and severity of dyspnea increase in the last weeks of life,[3] and it is the main symptom in more than 20% of patients in the last 48 hours of life.[4] In a multinational study of terminal sedation, dyspnea was the most frequent symptom prompting sedation in 25–53% of patients.[5] Similarly, in an Italian palliative care unit, 28% of cancer patients had intractable dyspnea at the end of life, which required heavy sedation.[6] These studies suggest that in the last weeks of life, current management strategies, although helpful, are not adequate for symptom control, resulting in more frequent need for hospitalization and heavy sedation.[1,6]

Dyspnea should be distinguished from respiratory failure, which is defined as hypoxia and/or hypercapnia. The American Thoracic Society consensus statement defines dyspnea as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interaction among multiple physiologic, psychological, social, and environmental factors, and may induce secondary physiologic and behavioral responses."[7] This definition underlines the subjective and inherently multidimensional nature of dyspnea, and its impact on multiple domains of quality of life.[1] Like pain, dyspnea is a combination of sensation and perception, but in contrast to pain, the neural pathways underlying dyspnea are not well understood.[8] Anything that alters perception (pharmacological or nonpharmacological interventions) may improve the symptom. Clearly, opioids and anxiolytic agents work partially through this mechanism.[1] Currently, for terminally ill patients with advanced cancer, effective therapies targeting the sensation of dyspnea, for example reducing ventilatory demand or improving respiratory muscle strength, are lacking. Therefore, the mainstay of dyspnea palliation remains altering central perception, and morphine is still the first choice of pharmacological therapy.[8]

Many patients report anxiety concurrent with the feeling of breathlessness. Dyspnea can lead to anxiety, and anxiety can exacerbate dyspnea.[8] According to some authors,[8] although opioids may initially have anxiolytic properties, patients typically become tolerant to these effects, and for this reason, anxiolytics (such as benzodiazepines) may have a role in dyspnea management. Although some preclinical[9] and clinical trials[10,11] showed that under some conditions the concurrent use of opioids and benzodiazepines is safe, many physicians are still reluctant to use this combination because of their fear of respiratory depression.

A treatment for dyspnea should not only include measures to control baseline levels of the symptom, but also for controlling the breakthrough component. Particularly during the later episodes, patients experience intense anxiety (respiratory panic attacks), and in this setting, we speculated that a short-acting anxiolytic, such as midazolam, could be useful.

The present trial was designed to assess the role of midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception during the last week of life in patients with advanced cancer.

Methods

Study Design

The study protocol was reviewed and approved by the Research and Ethics Committees of the Angel H. Roffo Cancer Institute of the University of Buenos Aires, and was in accordance with the recommendations found in the Helsinki Declaration of 1975.

Patients were randomly assigned (using a random number generator in 1:1:1 ratio in blocks of nine) to one of the three treatment groups. The principal endpoints were dyspnea intensity (modified Borg scale)[12] and dyspnea relief (yes-no) after the intervention. Additional endpoints were episodes of breakthrough dyspnea (BD) requiring rescue medication (episodes/day), as well as frequency and severity of medication-related side effects. Patients who received morphine were systematically premedicated with laxatives.

Values are presented as mean with the 95% confidence interval (CI), or median with the interquartile range (IR). Unless otherwise noted, the Wilcoxon's signed rank test was used for intragroup comparisons, and the

Kruskal-Wallis one-way analysis of variance and/or Wilcoxon's rank sum test were used for intergroup comparisons. The *P* values cited were two sided, and *P* values less than 0.05 were judged as statistically significant. All calculations were done with the statistics program Statistix 7.0 (Analytical Software, Tallahassee, FL, USA, 2000).

Inclusion Criteria

Patients who could provide informed consent and who were 18 years of age or older, with a documented diagnosis of terminal advanced cancer, life expectancy less than a week, Mini-Mental Status Exam (MMSE) > 23/30, severe dyspnea at rest, and a performance status of 4 (Eastern Cooperative Oncology Group categorical scale, where 0 is "fully active" and 4 is "completely disabled"), were eligible.

Exclusion Criteria

Exclusion criteria included chronic obstructive pulmonary disease with hypercapnia, noncompensated congestive heart failure, severe renal or hepatic failure (clinically and/or biochemically detected), and other uncontrolled (numerical rating scale > 3/10) symptoms (excepting anxiety associated with dyspnea) that could require the use of opioids, benzodiazepines, glucocorticosteroids, phenothiazines, bronchodilators, or methylxantines.

Treatment Regimen

For patients receiving baseline opioids, the total daily opioid dose was calculated and converted to oral morphine equivalents. A 3:1 ratio was used to convert oral dose to subcutaneous dose of morphine. If the daily subcutaneous equivalent dose of morphine (DsEDM) was lower than 15 mg, then patients were considered opioid naïve. If the DsEDM was equal to or higher than 15 mg, patients received an increase in dose equal to 25% of their respective DsEDM.

Patients were randomized to receive around-the-clock morphine (2.5 mg every 4 hours for opioid-naïve patients or a 25% increment above the DsEDM for those receiving baseline opioids) with midazolam rescues (5 mg) in case of BD (Group Mo); around-the-clock midazolam (5 mg every 4 hours) with morphine rescue doses (2.5 mg) in case of BD (Group Mi); or around-the-clock morphine (2.5 mg every 4 hours for opioid-naïve patients or a 25% increment above the DsEDM) plus midazolam (5 mg every 4 hours) with morphine rescue doses (2.5 mg) in case of BD (Group MM) (Fig. 1). For all cases, rescue doses were administered with an interval equal to or greater than 15 minutes apart.

All drugs were given subcutaneously through a butterfly needle located in the infraclavicular space. Drug administrations were performed in a single-blind fashion. The treatment was suspended for patients who developed somnolence Grade 3 (patient sleeping between 6 and 11 hours during the day) or more at the moment of receiving the corresponding dose of medication.

All patients were treated in our hospital as inpatients and offered psychological, spiritual, and nonpharmacological support (air therapy, breathing therapy, relaxation exercises) by nurses or caregivers. None of the patients received oxygen therapy and/or steroids and/or pharmacological treatment to control respiratory symptoms during the study or prior to their inclusion.

Treatment drugs were purchased from the market and provided by the institutional pharmacy.

Assessment

The modified Borg scale from 0 (none) to 10 (maximal) was used to assess the intensity of dyspnea.[12] This was performed at baseline and at 24 and 48 hours after randomization. Dyspnea relief (yes/no) was assessed at 24 and 48 hours after the randomization. The number of episodes of BD needing rescue medication was assessed daily. The MMSE was performed for screening cognitive impairment. Oxygen saturation and oxygen partial pressure were monitored using pulse oximetry (arterial blood was used only if it was taken for other laboratory parameters during initial evaluation). Anxiety and other symptoms (including pain) were assessed using several numerical rating scales, ranging from 0 (no symptom) to 10 (highest level).

The National Cancer Institute Common Toxicity Criteria (CTC) version 2.0 was used to score treatment adverse events (AE). AE not included in the CTC were graded using the following definitions: Grade 1, mild; Grade 2, moderate; Grade 3, severe; and Grade 4,

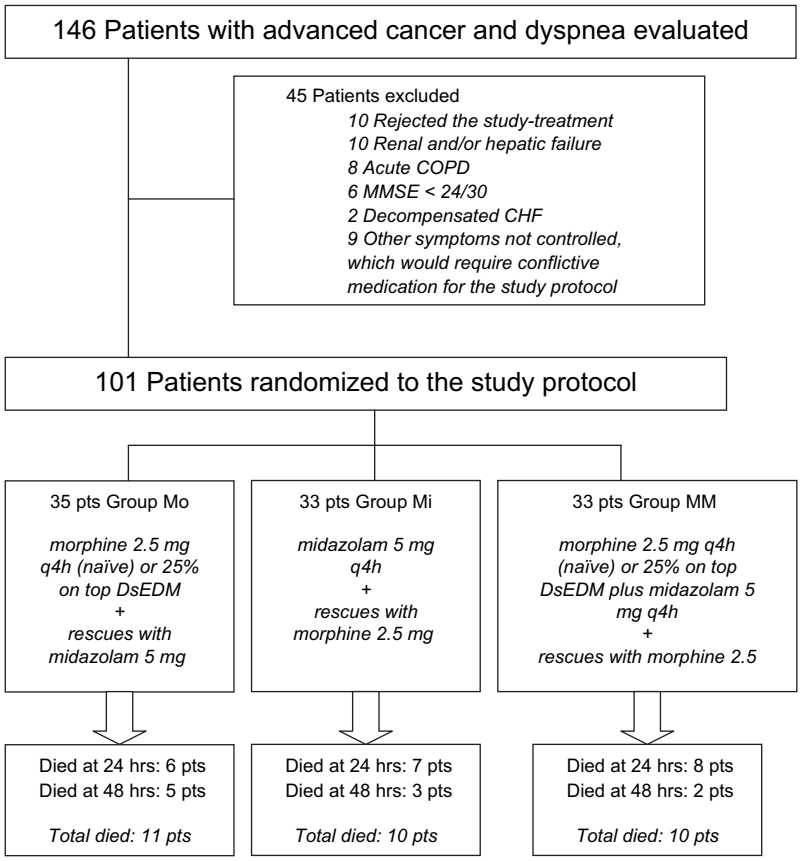

Fig. 1. Flow of patients during the study.

life-threatening. The principal investigator, in consensus with the treating team, made the decision as to whether a given AE was treatment related (unrelated, unlikely, possible, probable or definite) or not. All AE Grade 2 or higher, probably or definitely related to the treatment, were considered as clinically relevant. For scoring somnolence, we considered the time (in hours) that the patients spent sleeping during the daytime hours and the following criterion was used: Grade 1 (less than 3 hours), Grade 2 (3–5 hours), Grade 3 (6–11 hours), and Grade 4 (12 or more hours).

Signs and symptoms definitely related to the disease were not graded.

Results

One hundred and one advanced cancer patients with severe dyspnea were randomized into three different groups. Thirty-five patients were entered in the Mo Group, 33 entered in the Mi group, and 33 entered in the MM group. The characteristics of the patients included are shown in Table 1. The flow of participants through the trial is shown in Fig. 1.

There was a significant correlation (Spearman's correlation) between dyspnea and anxiety at baseline, 24 hours, and 48 hours ($R = 0.25$, $P = 0.038$; $R = 0.25$, $P = 0.040$; and $R = 0.36$, $P = 0.002$, respectively). There were no correlations between these two variables and other variables analyzed (oxygen saturation, oxygen partial pressure—available in 15/35 patients in Mo, 15/33 patients in Mi, and 12/33 patients in MM—and dyspnea relief).

Values (average $\pm$ 95% CI) for oxygen saturation at baseline, 24 hours, and 48 hours were 72% (68 ± 74), 72% (68 ± 75), and 70% (66 ± 74) for Mo; 73% (67 ± 74), 70% (67 ± 72), and 70% (67 ± 71.5) for Mi; and 73% (68 ± 75), 73% (69 ± 74), and 71.5%

Table 1
Patient Characteristics ($n = 101$) at the Time of Enrollment

	Morphine ($n = 35$)	Midazolam ($n = 33$)	Morphine + Midazolam ($n = 33$)
Age in years (mean)	57.3	57.8	56.9
Sex (M/F)	18/17	13/20	16/17
Primary tumor (n)			
Lung	12 (34.3%)	8 (24.3%)	10 (30.3%)
Breast	7 (20%)	6 (18.2%)	6 (18.2%)
Gynecologic	4 (11.4%)	5 (15.1%)	5 (15.1%)
Sarcomas	4 (11.4%)	3 (9%)	5 (15.1%)
Unknown primary	3 (8.6%)	4 (12.2%)	3 (9.1%)
Colorectal	3 (8.6%)	3 (9%)	1 (3.1%)
Others	2 (5.7%)	4 (12.2%)	3 (9.1%)
Intensity of dyspnea (mean ± SD)	7.1 ± .8[a]	6.9 ± 1[a]	6.8 ± .8[a]
Patients with any kind of airway/ lung affection	32 (91.4%)	29 (88%)	31 (94%)
Opioid-naïve patients	4 (11.4%)	4 (12.2%)	3 (9%)

SD = standard deviation.
[a]Not significant.

(67 ± 73) for MM (no significant differences for inter- or intragroup comparisons by *t*-test).

Dyspnea Relief

At the time of the first assessment (24 hours), the percentages of patients who experienced dyspnea relief were 69%, 46%, and 92% in the Mo, Mi, and MM groups, respectively ($P = 0.0004$ and $P = 0.03$ for MM vs. Mi and MM vs. Mo, respectively) (Fig. 2). The median values of dyspnea intensity (considering all the patients) were 3 (IR 2–5.5), 4 (IR 2–6.2), and 3 (IR 2–5) for Mo, Mi, and MM, respectively (P = NS for intergroup comparison). These values were statistically different from the baseline for each group ($P = 0.002$, $P = 0.018$, and $P = 0.003$ for Mo, Mi, and MM, respectively) (Fig. 3).

At the time of the second assessment (48 hours), the median values of dyspnea intensity (considering all the patients) were 2 (0–4.7), 2 (0–7), and 2 (1–5), respectively (P = NS for intergroup comparison). These values were statistically different from the baseline for each group ($P = 0.0001$, $P = 0.004$, and $P < 0.0001$ for Mo, Mi, and MM, respectively) (Fig. 3). Those with no dyspnea relief (no controlled dyspnea) represented 12.5%, 26%, and 4% for Mo, Mi, and MM, respectively ($P = 0.04$ for MM vs. Mi) (Fig. 4).

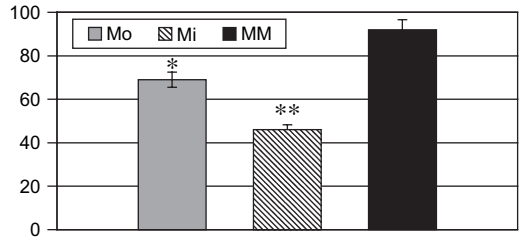

Fig. 2. Percentage of patients who experienced dyspnea relief at 24 hours. *$P = 0.003$ compared with MM. **$P = 0.0004$ compared with MM.

Breakthrough Dyspnea

The analysis of episodes of BD and the number of rescue medications was performed only for those patients who lived the full 24 or 48 hours. During the first day, the percentages of patients with BD for the groups Mo, Mi, and MM were 34.3%, 36.4%, and 21.2%, respectively (P = NS), and the numbers of episodes per patient (median, first-third quartile) were 2 (1–3.8), 1 (1–2.4), and 1 (1–1), respectively ($P = 0.027$ for Mo vs. MM, other comparisons NS) (Fig. 5). During the second day, the percentages of patients with BD for the groups Mo, Mi, and MM were 38%, 38.5%, and 24%, respectively (P = NS), and the numbers of episodes per patient (median, first-third quartile)

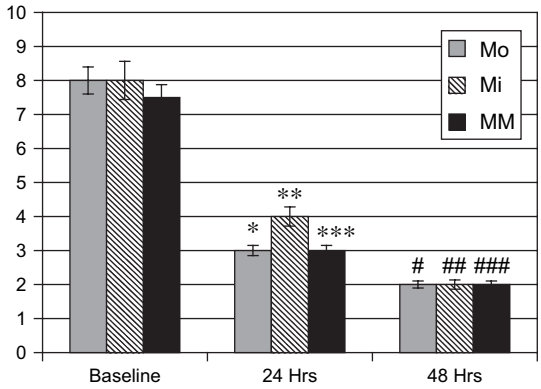

Fig. 3. Dyspnea intensity (Borg scale) at 24 and 48 hours (median). *$P = 0.002$, **$P = 0.018$, ***$P = 0.003$ compared with their respective baseline values. #$P = 0.0001$, ##$P = 0.0004$, ###$P < 0.0001$ compared with their respective baseline values.

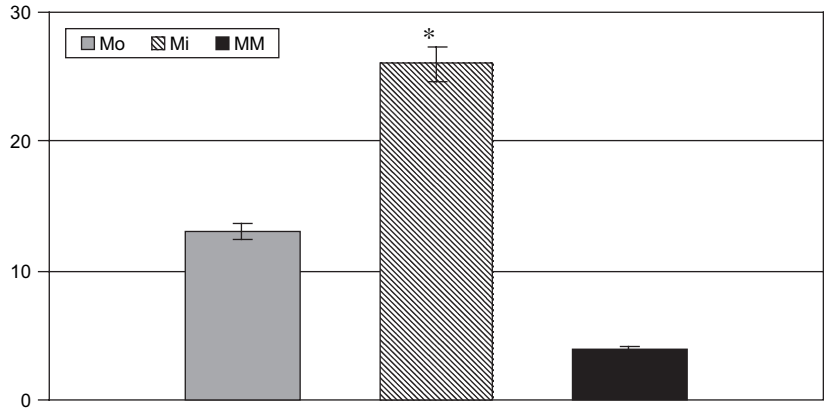

Fig. 4. Percentage of patients with persistent, uncontrolled dyspnea at 48 hours. *$P = 0.04$ compared with MM.

were 2 (1–4), 1 (0.75–1.25), and 1 (0.25–1.5), respectively ($P = 0.037$ for Mo vs. MM, $P = 0.034$ for Mo vs. Mi, and $P =$ NS for MM vs. Mi) (Fig. 5).

Adverse Events

Forty-five AE were recorded (Table 2). Of these, only 17 were clinically relevant (Grade 2 or higher) and morphine plus midazolam rescues (i.e., the Mo group) caused more distressing side effects (11/17) compared with the other two treatment modalities (3/17 each of them) ($P = 0.0324$, Fisher's exact test). The most frequently recorded AE was somnolence, which was present at clinically relevant grades in 17%, 6%, and 9% for Mo, Mi, and MM, respectively.

Discussion

Dyspnea is one of the most frightening and distressing symptoms for cancer patients and their families; nevertheless, it is frequently neglected by caregivers. A study of late-stage cancer patients found that almost 62% of patients with dyspnea had been symptomatic for more than 3 months and that the majority of them had received no medical or nursing intervention to control their breathlessness.[13] Unfortunately, at the present time, no successful physiopathological intervention exists (i.e., modifying sensation) for most patients with far-advanced cancer. Thus, pharmacologic and nonpharmacologic interventions that alter perception continue to be the principal palliative measure.

Since dyspnea is rarely stable at the end of life, it is imperative to plan an adequate strategy for the breakthrough component. BD is defined as an acute increase in breathlessness to a level greater than the patient's well-controlled baseline level. BD is usually brief, with a sudden or gradual onset, leading to a high level of anxiety (usually called respiratory panic attacks) and may appear spontaneously or be

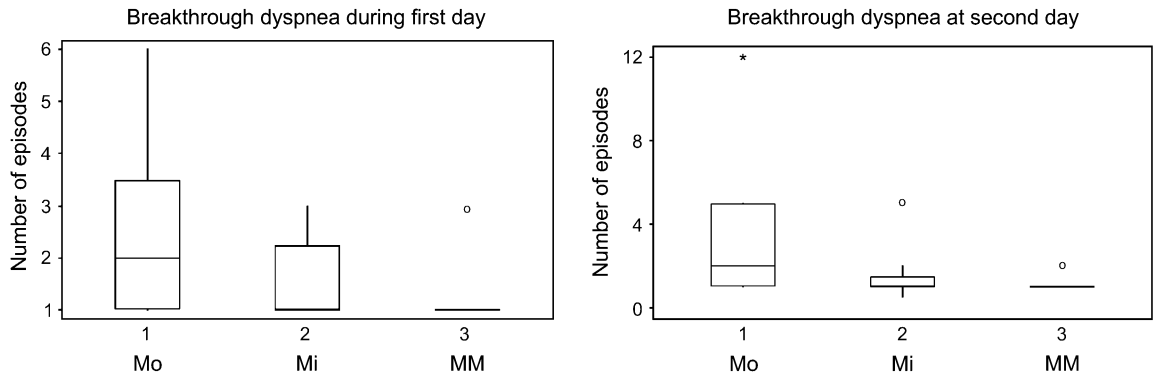

Fig. 5. Episodes of BD.

Table 2
Side Effects Probably or Certainly Related to the Treatments

	Morphine ($n=35$)	Midazolam ($n=33$)	Morphine + Midazolam ($n=33$)
Somnolence			
Grade 1	5	5	4
Grade 2	4	2	2
Grade 3	2	None	1
Unsteadiness	None	3 (Grade 1)	None
Nausea/vomiting			
Grade 1	1	1	4
Grade 2	4	1	None
Puncture site	1 (redness Grade 1)	1 (itching Grade 1)	None
Others	1 (xerostomia Grade 1) 1 (dizziness Grade 1)	1 (myoclonus Grade 1) 1 (hallucinations Grade 1)	None
Patients with clinically relevant toxicity	10 (29%)[a]	3 (9%)[a]	3 (9%)[a]

[a] $P=0.0412$, Pearson's Chi-square.

precipitated by a trigger. These episodes are, in particular, highly distressing for the patients and their caregivers.

According to a recent review on opioids for palliation of dyspnea,[14] there is a statistically significant benefit for non-nebulized opioids in dyspnea management. Although several opioids are generally used, morphine remains the mainstay of pharmacology therapy for dyspnea.[1,8] Nevertheless, there is no standard dose, schedule, or route of administration. A small trial showed that a morphine dose of 5 mg every 4 hours delivered subcutaneously for opioid-naïve patients was useful and safe for controlling dyspnea.[15] For patients receiving baseline opioids, a 25% increase in the baseline dose provided relief for up to 4 hours.[16] In a previous trial by our group comparing oxygen therapy vs. morphine for dyspnea in 51 patients with advanced cancer,[11] those entered in the morphine group received 2.5 mg subcutaneously every 4 hours. After 24 hours, 72% of them required dose escalation to 5 mg subcutaneously every 4 hours because of poor control with the starting dose. Although dose escalation led to a better control of the symptom, the frequency of AE was higher. Since we designed this trial to determine the role of midazolam as a component of a combination therapy, a conservative approach regarding dose was followed. Thus, we decided to administer morphine subcutaneously at a dose of 2.5 mg every 4 hours (or as a rescue dose) or increase it to 25% for those on baseline opioids.

Shortness of breath in cancer patients is usually accompanied by variable degrees of psychological distress manifested as anxiety, fear, panic, and a sensation of impending death. The relationship between breathlessness and psychological symptoms (such as anxiety)[17] leads to the suggestion that a beneficial therapeutic strategy for dyspnea might include intervention for psychological distress.[18] Some authors suggest that although opioids may initially have anxiolytic properties, patients may become tolerant to these effects.[8,19] In this context, animal studies showed how midazolam is able to inhibit morphine tolerance[20,21] and withdrawal[22] by affecting some of the changes induced in the brain by morphine. The pharmacological actions of midazolam are identical to those of other benzodiazepines, including sleep induction, sedation, anxiolysis, and amnesia.[23] Midazolam differs from other agents by virtue of its more rapid onset of clinical effects and shorter duration of action and is broadly used for conscious sedation (combined or not with an opioid).[23–25] In palliative care units, midazolam is commonly administered by subcutaneous infusion at a dose ranging approximately between 10 and 60 mg/day, often in association with morphine.[26] The absolute bioavailability of subcutaneous midazolam is about 96%[27] and the local tolerance is generally good.[28]

Theoretically speaking, opioids for dyspnea treatment can be administered orally, rectally,

sublingually, subcutaneously, intravenously, and by inhalation, but during the final hours of life when the ability to swallow declines and consciousness wanes, rectal, subcutaneous, and intravenous routes are more commonly used.[29] In recent years, the subcutaneous route has been demonstrated to be an effective and well-tolerated method for parenteral administration of drugs[26,30] and hydration in palliative care.[31,32] The subcutaneous route has many advantages over other parenteral ones. For example, it can usually be managed by relatives and caregivers, enabling terminally ill patients to be looked after at home rather than being hospitalized.

Benzodiazepines like lorazepam, diazepam, and midazolam are frequently prescribed empirically to relieve dyspnea in cancer patients. However, several small-scale controlled studies performed in other populations gave inconsistent results, and anxiolytics tend to be poorly tolerated.[7] The present study showed that the beneficial effects of morphine in controlling baseline levels of dyspnea may be improved with the addition of midazolam to the treatment. The number of BD episodes when patients received both drugs from the beginning (MM group) was lower than that in the other two groups (Mo and Mi). During the first 24 hours, dyspnea was better controlled in those patients receiving the combination of drugs on an around-the-clock basis. This group also had fewer patients (only 4%) with uncontrolled dyspnea at 48 hours. Thus, midazolam was more likely to increase the efficacy of morphine in controlling dyspnea when both drugs were administered together.

Interestingly, the median daily values for dyspnea reported from patients were similar among groups; nevertheless, the number of episodes of BD recorded from the same patients was different. This fact underlines the importance of assessing both components of the symptom (chronic and breakthrough).

One potential limitation of our study is the single-blinded nature of the design. The treating physicians' knowledge of which schedule of drugs the patient received could influence their need for administering rescue medications. A double-blind design can avoid this, but was considered not appropriate for our study population by the Ethics Committee at our institution. Nevertheless, the risk for underestimation of rescue needs was minimized by a double assessment of breakthrough episodes carried out by caregivers and research physicians.

In spite of these results being significant, clinicians should prescribe this combination for the control of dyspnea in advanced cancer patients with care. Our data imply that AE were minimal considering the relief. Neither severe sedation nor severe respiratory depression was identified. However, it should be noted that most of our participants had already taken opioids, which is a highly common situation at the end of life. For opioid-naïve patients, a dose-titration scheme should be considered. There were no statistically significant differences between treatment groups regarding mortality rates at any point. Aside from this fact, it is very difficult to know, with an acceptable degree of certainty, the ultimate cause of death in this population of actively dying patients. We were unable to detect severe respiratory depression in any group and considering that the in-treatment deaths were not temporally related with the drug administration, we believe that the possibility of the mortality being due to respiratory depression was low, and that most of them were related to the underlying advanced disease.

Interestingly, both groups that received around-the-clock midazolam showed fewer AE, particularly less nausea/vomiting. This finding is in accordance with several reports regarding the antiemetic property of midazolam;[33–35] nevertheless, this drug does not appear to have earned a niche in the antiemetic armamentarium for the symptomatic management of patients.[36] Somnolence was also higher among patients in the morphine group than among patients in the other two groups. Analyzing the data, we can assume that this higher incidence in the morphine group was more likely a consequence of the relatively poor control of BD in some patients in this group. Particularly, patients who presented with the higher grades of somnolence had presented a median of 7 daily episodes of BD (ranging from 5 to 12), which resulted in receiving a higher dose of midazolam, in the form of rescues, than those patients in the other two groups.

Conclusion

The present study shows that the beneficial effects of morphine in controlling baseline levels of dyspnea could be improved by the addition of midazolam to the treatment. A study to show if midazolam could have a role in the management of long-term dyspnea in less terminally ill patients with cancer is actually ongoing in our unit.

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