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ORIGINAL ARTICLE

Fentanyl treatment for end-of-life dyspnoea relief in advanced cancer patients

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Abstract

Purpose We assessed the effects of subcutaneous-endovenous fentanyl on dyspnoea in a cohort of advanced cancer patients.

Methods We performed a retrospective study in a cohort of advanced cancer patients with dyspnoea at rest who received subcutaneous or intravenous fentanyl. Patients with no shortness of breath at rest or at minimal exertion, no rescue doses per 24 h, were deemed to be responders to fentanyl. The period of assessment was 6 days from the beginning of fentanyl treatment.

Results Seventy-two patients were evaluated: 65% males, 50% ≥ 75 years, Palliative Performance Scale (PPS) median of 30%. Seventy-six percent of the patients were responders to fentanyl. Fentanyl efficacy was not statistically related to age, gender, cancer type, previous opioid treatment, steroid and midazolam doses and PPS. The median fentanyl dose in responders was 25 mcg/h (interquartile range 12–70). It was significantly related to age (37 vs 12 mcg/h, for ≤ 75 vs > 75 years, respectively; $p = 0.02$). There was not a significant difference between fentanyl doses of responders and non-responder patients. Thirty-six, 23 and 15 patients had sustained improvements in dyspnoea over 48, 72 and 96 h. Fentanyl had no significant toxicity. The length of inclusion in the study and exclusion were related to low performance status (hazard ratio 0.961; $_{95\%}$CI 0.927–0.996; Cox-regression) but not to fentanyl doses (hazard ratio 0.875; $_{95\%}$CI 0.620–1.234; Cox-regression).

Conclusion Our preliminary data suggest that subcutaneous-endovenous fentanyl may be associated with dyspnoea relief in dying patients. Further research is needed to confirm these findings.

Keywords Fentanyl · Dyspnoea · Subcutaneous fentanyl · Endovenous fentanyl · Refractory dyspnoea · Palliative care

Introduction

A range of distressing symptoms affect cancer patients and some, such as breathlessness, worsen as the patient approaches death [1–3]. Little is known about breathlessness in the last week of life, including any treatment that may help to relieve the distress associated with dyspnoea. Because of its prevalence, the level of suffering it causes and the lack of treatment options, refractory dyspnoea management plays an important part in palliative care and is a research area of relevance [4–6].

Opioids are considered the cornerstone of palliative management of chronic refractory dyspnoea [5, 7], but the evidence of their efficacy is controversial [8, 9]. Oral morphine is the most studied opioid in dyspnoea treatment across the trajectory of the condition and there is some evidence of its efficacy. However, data on the efficacy of other opioids and modes of delivery are sparse [10, 11]. Moreover, there are no robust data on the efficacy of opioids for managing dyspnoea in dying patients [12].

Fentanyl is a synthetic μ-opioid that is currently approved for the management of baseline and breakthrough pain. It presents the advantages of no renal elimination, transdermal delivery and other modes of delivery [13]. Several series of cases of oral transmucosal fentanyl citrate and intranasal fentanyl reported some benefits in dyspnoea crises, but the evidence of their efficacy is controversial because of certain methodological limitations of the studies [11, 14–16]. A better

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understanding of the effect of intravenous or subcutaneous fentanyl on dyspnoea may help us to better manage this distressing symptom in dying patients.

In our unit, intravenous or subcutaneous fentanyl is a treatment option for pain and dyspnoea in patients with a high risk of developing opioid side effects in response to escalating doses in the presence of deteriorating renal function, or to avoid potential side effects resulting from opioid rotation from or to transdermal fentanyl. The objective of this retrospective study was to assess the efficacy and safety of a protocol for dyspnoea relief with intravenous or subcutaneous fentanyl in a cohort of patients admitted to our palliative care unit.

Patients and methods

We evaluated the efficacy of continuous intravenous or subcutaneous fentanyl on dyspnoea in a cohort of advanced cancer and non-cancer patients. Intravenous or subcutaneous fentanyl was considered as a treatment option in patients with breathlessness at rest or severe at minimal exertion in the following clinical conditions: (a) a decline in renal function (MDRD-estimated glomerular filtration rate below 40 mL/min) in the presence of escalating doses of transdermal fentanyl or another opioid and (b) as an alternative to transdermal fentanyl in patients at discharge. Informed consent for fentanyl treatment was obtained from all patients or their families as per our routine management of advanced cancer patients. Since clinical data were collected routinely, separate consent for this research was not required. The study protocol was approved by the Human Research Ethics Committee of Hospital Universitario La Candelaria.

Parenteral fentanyl protocol

The starting fentanyl dose was equivalent to previous opioid treatment plus 30–50%, in old and young patients, respectively. The intravenous or subcutaneous fentanyl doses were then calculated applying a 1:1 ratio from transdermal fentanyl, or a 1:66 ratio from parenteral morphine (or equivalent doses of oxycodone or hydromorphone) [17, 18]. Following previous opioid treatment withdrawal, continuous intravenous or subcutaneous fentanyl was started 4–6 h later, to prevent opioid overdose during the transition from previous opioid treatment to intravenous or subcutaneous fentanyl.

The starting fentanyl dose was titrated upwards or downwards every 24 h by 30–50%, depending on patient satisfaction with breathlessness relief and side effects. Rescue doses of 10% of the daily fentanyl dose were given as required to manage dyspnoea crises every 30 min during both fentanyl clearance, to avoid a therapeutic gap, and intravenous or subcutaneous fentanyl treatment. Adjuvant drugs, previously administered to control symptoms caused by illness or treatment, were continued at the same dose. Anxious patients received midazolam treatment, 10–15 mg/day; hypoxemic patients received oxygen therapy.

Throughout the fentanyl treatment, the patients underwent routine clinical assessment every morning by one or more of the seven full-time palliative care units' experienced physicians. The physician assessment included the Edmonton Symptom Assessment System and the evaluation of other clinical signs, including myoclonus, hallucinations, delirium, respiratory rate and digital oxygen saturation. Cognitive status was assessed by Mini-Mental State Examination or the Pfeiffer Short Portable Mental Questionnaire Status, depending on the clinical condition of the patients. Delirium diagnoses were based on criteria from the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders. Symptom intensity was assessed by patients using the standard four-point verbal rating scale (none, mild, moderate and severe). Attending palliative nurses monitored every 2 h breathlessness and somnolence-sedation levels (assessed on a 0–4 scale: 0 awake, 1 slight somnolence, 2 aroused by voice, 3 unarousable and 4 unarousable with clinical signs of respiratory depression). Other potential side effects reported by patients during fentanyl treatment were collected too. All patients were admitted for the duration of parenteral fentanyl treatment. Patients with no dyspnoea at minimal exertion during 5 days were switched to transdermal fentanyl and discharged.

Data collection

The following data were collected for each patient: age, gender, primary tumour site, clinical situation prior to fentanyl treatment, reason for intravenous or subcutaneous fentanyl treatment, dyspnoea intensity at rest and at minimal exertion, number of daily rescue doses used for dyspnoea crises, fentanyl doses in relation to treatment outcome, time to achieving satisfactory breathlessness relief, fentanyl side effects and survival time. Other symptoms assessed in regular clinical evaluation were not included in analysis of the data. Patients in whom it was difficult to assess symptom intensity derived from mental deterioration were excluded from the study.

The outcome of treatment with fentanyl was determined daily during 6 days. The day prior to intravenous or subcutaneous fentanyl was defined as T0 and the following days, after 24, 48, 72, 96, 120 and 144 h of parenteral fentanyl treatment, as T1, T2, T3, T4, T5 and T6, respectively. For the purpose of the study, dyspnoea intensity was classified on a four-point scale based on patient self-reports and fentanyl rescue doses for dyspnoea crises over the previous 24 h: level 1 (no shortness of breath at rest nor at minimal exertion, no rescue doses per 24 h), level 2 (no breathlessness at rest, mild dyspnoea at minimal exertion and 1–2 rescue doses per 24 h), level 3 (mild dyspnoea at rest plus mild-to-moderate dyspnoea at minimal

exertion and 3–4 rescue doses per day) and level 4 (mild-to-moderate baseline dyspnoea plus mild-to-severe dyspnoea at minimal exertion and more than 4 rescue doses per 24 h). We evaluated the characteristics of patients who experienced response and sustained response to fentanyl. Patients were deemed to be "responders" to fentanyl when their dyspnoea intensity was equivalent to level 1 over 24 h or longer at any time during the study. For the statistical analysis, we classified as "non-responder" those patients with partial improvement of their dyspnoea up to level 2 and patients with dyspnoea level 3 or 4 who did not improve. Improvements in dyspnoea to level 1 over periods of more than 24 h were classed as "sustained response to fentanyl" and described according to the duration of the sustained response, over 48 and 72 h or longer. Patients were deemed to be evaluable if they were in the study for 24 h or more before being excluded due to a worsening clinical condition.

Data analysis

We used descriptive statistics, mean, standard deviation, median, interquartile range and percentages to summarise population characteristics, breathlessness and adverse events. We used Student *T* test, ANOVA, Tukey tests and Cox-regression for the statistical analyses of parametric variables and x^2, Mann-Whitney and Kruskal-Wallis tests for non-parametric variables. Differences resulting in *P* values of less than 0.05 were considered to be statistically significant. All data were analysed using the SPSS software program (for Windows, version 21, SPSS Inc., Chicago, USA).

Results

Between January and December 2014, 640 patients with advanced cancer and 16 dying non-cancer patients were admitted to the tertiary Palliative Care Unit at Hospital La Candelaria, because of severe symptom distress requiring medical intervention. Two hundred seventy-four patients, 41.7% of the 656, received intravenous or subcutaneous fentanyl as opioid treatment during the admission, 72 of them for dyspnoea. Table 1 summarises the most relevant characteristics of these patients. Previous transdermal fentanyl treatment was the main reason for choosing continuous intravenous or subcutaneous fentanyl. Forty-one patients (57% of 72) received dexamethasone 8 mg/day and 27 (37% of 72) midazolam 10 mg/day. The median of starting fentanyl doses was 25 mcg/h (interquartile range 12–37). Doses were not significantly different between gender and cancer type. Older patients started the treatment with the lower doses ($p < 0.01$).

Table 2 describes the patients' clinical situations at different stages of the study. The total percentage of responders to intravenous or subcutaneous fentanyl was 76%: 47 patients were responders at T1 and 8 were responders during the following days. Nine patients experienced a partial response to fentanyl (12% of 72): seven patients at T1 and two during the following days improved their dyspnoea up to level 2. Five patients (7% of the initial cohort), 4 with dyspnoea level 4 and 1 with dyspnoea level 3, did not achieve any relief before being excluded from the study at T1, and three patients (4% of the initial cohort) gained only slight improvement up to level 3 dyspnoea (2 patients at T1 and 1 at T2). The number of patients evaluated fell during the study, namely 67, 48, 36, 28, 18 and 12 at T1, T2, T3, T4, T5 and T6, respectively; which represents an attrition rate of 81.9%. The main reasons for exclusion from the study were worsening clinical situations, namely respiratory failure and signs of impending death, delirium or death. Only four patients (5.5%) could be discharged during the study with no dyspnoea at minimal exertion.

Table 1 Characteristics of initial cohort ($n = 72$)

Characteristics	*n* (%)	Characteristics	*n* (%)
Sex		Treatment with	
Male	47 (65%)	Dexamethasone	41 (57%)
Female	25 (35%)	Midazolam	27 (37%)
Age (years)		Fentanyl:	
< 75	36 (50%)	- Subcutaneous	11 (15%)
75–80	15 (21%)	- Endovenous	61 (85%)
≥ 80	21 (29%)		
Primary cancer		PPS (median, Q1-Q3)	30 (20–40)
Genitourinary	8 (11%)	Clinical signs (mean ± sd)	
Gastrointestinal	21 (29%)	Respirations per min	23 ± 5
Lung	20 (28%)	Beat per min	93 ± 18
Head and neck	5 (7%)	O_2 saturation	93% ± 5
Others	13 (18%)	Blood pressure, mmHg	124 ± 23
Non-cancer	5 (7%)		72 ± 22
Metastases			
Lung	6 (8%)		
Liber	3 (4%)		
Bone	3 (4%)		
Brain	2 (2%)		
Spread	27 (37%)		

PPS palliative performance scale, *Q1-Q3* quartiles

The median of dosages of responder patients with intravenous or subcutaneous fentanyl was 25 mcg/h (interquartile range 12–62.5). There was not a significant difference in fentanyl doses between of responders and non-responder patients (median of dosages 25 mcg/h; interquartile range 12–63.4; $p = 0.5$). Response to fentanyl was not statistically related to the collected variables (Table 3).

Tables 4 and 5 describe patients with sustained response to fentanyl treatment on dyspnoea. Fifteen out of 28 evaluable patients were on dyspnoea level 1 over 96 h, 23 out of 36 were

Table 2 (a) Clinical status of patients at different times during the study; (b) description of periods when patients responded to fentanyl. $N = 72$ patients

a)	Time (days)						
	T0	T1	T2	T3	T4	T5	T6
Patients in the study							
Dyspnoea level 1	–	47 (70%)	36 (75%)	26 (72%)	18 (64%)	12 (67%)	8 (67%)
Dyspnoea level 2	–	9 (13%)	8 (17%)	6 (16%)	3 (11%)	2 (11%)	2 (17%)
Dyspnoea level 3	14 (19%)	3 (5%)	2 (4%)	2 (6%)	3 (11%)	2 (11%)	1 (8%)
Dyspnoea level 4	58 (81%)	8 (12%)	2 (4%)	2 (6%)	4 (14%)	2 (11%)	1 (8%)
Total	72	67	48	36	28	18	12
Excluded patients							
Delirium	–	5	18	14	12	11	7
Deceased	–	0	6	22	32	43	49
Discharged	–	0	0	0	0	0	4
Total	–	5	24	36	44	54	60

b)	Time (days)							*N (%)*
	T0	T1	T2	T3	T4	T5	T6	
Responders (dyspnoea level 1)		47	7	1	–	–	–	55 (76%)
Partial responders (dyspnoea level 2)		7	2	–	–	–	–	9 (12%)

on level 1 over 72 h, and 36 out of 48 were on level 1 over 48 h. The sustained responses to fentanyl were not statistically related to fentanyl doses and the other collected variables.

At T1, 100% of the patients were awake during day-time and aroused by voice at night-time. Fentanyl, at the doses given in the study, was well tolerated with no documented withdrawal due to somnolence-sedation or other toxicity. Median fentanyl doses among the patients who remained in the study at T6 were statistically higher than among those who died (37 vs 18 mcg/h; $p < 0.05$ Mann-Whitney test). The duration of the patients in the cohort before exclusion due to delirium, palliative sedation or death was statistically related to low performance status (hazard ratio 0.961; $_{95\%}$CI 0.927, 0.996; $p < 0.02$ Cox-regression) but not statistically related to fentanyl dosing (hazard ratio 0.875; $_{95\%}$CI 0.620, 1.234; $p = 0.4$ Cox-regression).

Discussion

In this retrospective study, we assessed the efficacy of fentanyl on dyspnoea at rest in advanced cancer patients. Ours is the first large study to demonstrate the long-term effect of intravenous or subcutaneous fentanyl on baseline breathlessness over more than 24 h in dying patients. Our data suggest considering fentanyl as an opioid option for the relief of breathlessness in terminal cancer patients.

We established a four-tier scale of intravenous or subcutaneous fentanyl outcomes: from level 1, understood as dyspnoea-free, both at rest and upon minimal exertion and with no rescue dose for breathlessness exacerbations, to level 4, with dyspnoea at rest and several moderate-to-severe crises per day. Criteria were developed to assess in a retrospective study the effect of opioids on the complex and fluctuating phenomenon of end-of-life dyspnoea. Other measurements to assess the opioid effect have been used in specific situations, such as dyspnoea at rest, dyspnoea with exertion and dyspnoea crises, but there is no international consensus on how to best evaluate the pharmacological management of breathlessness [5, 19].

In our study, intravenous or subcutaneous fentanyl improved dyspnoea at rest and reduced dyspnoea exacerbations in a significant proportion of patients. We assumed that a good response to fentanyl could be expressed as dyspnoea relief, both at rest and at minimal exertion, and a reduction in exacerbations. To our knowledge, this assumption has not yet been proved, although this effect was in line with the findings of Navigante et al. [20]. In both studies, the control of dyspnoea at rest with opioids seemed to affect the development of crises. Thus, such as occurs in the management of cancer pain, opioid under-treatment of baseline symptoms, like pain or dyspnoea, could be responsible for several exacerbations of baseline symptoms other than incidental or breakthrough pain [21].

Our study found a high proportion of patients responding to fentanyl in the last week of life: about 76% at different times across the duration of the study. This is in accordance with the findings from other investigations into the effect of morphine on dyspnoea control in the last week of life in cancer and non-cancer patients [20, 22]. Moreover, to our knowledge, this is the first study to show a sustained effect of fentanyl on

Table 3 Description of the responder/non-responder patients to fentanyl at T1 or the following days of the study[a]

Characteristics	Responders ($N = 55$)	Non-responders ($N = 12$)	p value
Sex			0.843
Male	35 (64%)	8 (67%)	
Female	20 (36%)	4 (33%)	
Age (years)			0.116
< 75	25 (46%)	8 (67%)	
75–80	15 (27%)		
≥ 80	15 (37%)	4 (33%)	
Primary cancer			0.783
Genitourinary	7 (13%)	1 (8%)	
Gastrointestinal	15 (27%)	4 (33%)	
Lung	15 (27%)	2 (17%)	
Head and Neck	3 (6%)	2 (17%)	
Others	11 (20%)	2 (17%)	
Non-cancer	4 (7%)	1 (8%)	
Metastases			0.117
Lung	3 (6%)	3 (25%)	
Liber	2 (4%)	1 (8%)	
Bone	2 (4%)	1 (8%)	
Brain	2 (4%)		
Spread	19 (34%)	6 (50%)	
PPS (median, Q1–Q3)	30 (20–40)	30 (30-30)	0.362
Clinical signs (mean ± sd)			
Respirations per min	22 ± 5	25 ± 7	0.057
Beat per min	93 ± 20	96 ± 12	0.672
O_2 saturation	92% ± 4	98% ± 11	0.246
Blood pressure, mmHg	127 ± 24	120 ± 19	0.404
	74 ± 16	70 ± 16	0.429
Treatment with			
Dexamethasone	33 (60%)	7 (58%)	0.973
Midazolam	22 (40%)	4 (33%)	0.753
Fentanyl			0.852
-Subcutaneous	8 (15%)	2 (17%)	
-Endovenous	47 (85%)	10 (83%)	

[a] Six of 72 patients were excluded of the study at T1

dyspnoea in dying patients: 75, 64 and 54% of evaluable fentanyl responders experienced a sustained response over 48, 72 and 96 h. Opioids, principally morphine, have shown a beneficial effect on dyspnoea in cancer and non-cancer patients. Data for the effectiveness of fentanyl on dyspnoea are contradictory. A systematic review performed by Simon et al. [11] and a later study undertaken by Pang et al. [23], in a sample of 16 dying cancer patients, found weak or no evidence for the effectiveness of fentanyl. However, more recent studies performed by Hui et al. and Simon et al. reported that fentanyl buccal tablet was more effective in the treatment of episodic dyspnoea than morphine and placebo and also effective in the prophylaxis of dyspnoea [24–27]. The findings of these recent studies, together with ours regarding the effect of fentanyl on dyspnoea at rest, provide information about the efficacy of fentanyl on dyspnoea.

Our study did not find that the effect of fentanyl was related to any potential effects of dexamethasone or midazolam on dyspnoea. Maeda et al. found benefits in the dexamethasone-morphine association on dyspnoea relief in a retrospective study of 20 advanced cancer patients [28]. Their study did not show benefits from fentanyl or oxycodone or its combinations with dexamethasone. Recently, Hui et al. reported the efficacy of dexamethasone, and the efficacy of the placebo too, in a double-blind, randomised, controlled trial in patients with a good performance status [29]. Mori et al. found in a prospective multicentre study carried out in 72 cancer patients that a relative good performance status, expressed as Palliative Prognostic Index < 6, and higher intensity dyspnoea were factors that significantly predicted the efficacy of dexamethasone [30]. Regarding the effect of midazolam, Navigante et al. found in a randomised controlled trial that a morphine-midazolam combination was significantly more effective in managing dyspnoea than treatment with either morphine or midazolam [20]. This was in line with the lack of effect of midazolam found in a randomised double-blind, multi-dose, placebo-controlled study of intranasal midazolam on breathlessness episodes, conducted by Hardy et al. and a recent Cochrane review [31, 32]. We cannot exclude that our data on the effects of dexamethasone and midazolam on dyspnoea were affected by the low weight of our sample. This limitation precluded the statistical analysis of patient subgroups to evaluate specifically the effect of dexamethasone and midazolam. The said data, together with our results, underline that the relative importance of these drugs is not clear and that further research is needed to understand their role in the treatment of dyspnoea in dying patients. Meanwhile, available data regarding the different responses of breathlessness to opioids have suggested that low dyspnoea intensity could be associated with better response to opioids in cancer patients and lower age and severe baseline dyspnoea in non-cancer patients [33, 34]. However, we did not identify any specific characteristic associated with an improvement in breathlessness derived from fentanyl treatment.

In our study, intravenous or subcutaneous fentanyl showed no severe side effects, treatments were not stopped and the patient's clinical deterioration was assumed by attending physicians to be the consequence of the progression of the life-limiting illness. Eighty-two percent of the patients dropped-out or died during the study, which reflects the degree of illness of the patients involved and their advanced stage of disease. Despite this, we found no influence of fentanyl on mortality. The main risk factor associated with drop-out resulting from respiratory failure, delirium or mortality was the low performance status, which is in accordance with the

Table 4 Description of fentanyl doses in responder patients with dyspnoea level 1 over 48 h or more (sustained response to fentanyl) during the study

Dyspnoea level 1	Patients *n* (%)		Fentanyl doses mcg/h Median (interquartile range)		*p* value
	Sustained effect		Sustained effect		
	Yes	No	Yes	No	
Over 48 h	36 (75%)	12 (25%)	25 (12.5–50)	49 (18.7–68.7)	0.173
Over 72 h	23 (64%)	13 (36%)	25 (12.5–50)	50 (25–75)	0.124
Over 96 h	15 (54%)	13 (46%)	25 (12.5–50)	25 (25–70.8)	0.198

Dyspnoea level 1 (no shortness of breath at rest nor at minimal exertion, no rescue doses per 24 h)

findings of Hui et al. in their research into the symptoms of advanced cancer patients in the last week of life [35].

Our study has several limitations that justify a cautious interpretation of the findings. First, our findings may not be generalisable to other settings, since patients were recruited from a single tertiary palliative care centre. Second, the small sample and the high attrition rate precluded robust statistical analysis to characterise the effect; this could increase the chance of false positives. Third, the inherent limitations of retrospective studies, such as the unblinded design, allowing unconscious biases to creep into the assessments and the random fluctuations in the clinical conditions of the study. Fourth, given the absence of a control group, we cannot exclude a powerful placebo effect associated with the switching of patients from oral/transdermal opioids to endovenous/subcutaneous fentanyl. However, it should be noted that the

Table 5 Characteristics of the patients with sustained response to fentanyl (dyspnoea level 1)

Characteristics	Over 48 h (*N* = 36)	Over 72 h (*N* = 23)	Over 96 h (*N* = 15)	*p* value
Sex				0.731
Male	21 (58%)	11 (48%)	8 (53%)	
Female	15 (42%)	12 (52%)	7 (47%)	
Age (years)				0.951
< 75	16 (44%)	12 (52%)	7 (46%)	
75–80	9 (25%)	4 (17%)	4 (27%)	
≥ 80	11 (31%)	7 (31%)	4 (27%)	
Primary cancer				0.942
Genitourinary	5 (14%)	5 (22%)	4 (27%)	
Gastrointestinal	12 (33%)	9 (39%)	5 (33%)	
Lung	7 (20%)	3 (13%)	3 (20%)	
Head and neck	1 (3%)	–	–	
Others	8 (22%)	5 (22%)	3 (20%)	
Non-cancer	3 (8%)	1 (4%)	–	
PPS (median, Q1–Q3)	30 (20-40)	30 (20-40)	30 (30–40)	0.987
Clinical signs (mean ± sd)				
Respirations per min	21 ± 6	20 ± 6	20 ± 7	0.665
Beat per min	92 ± 18	94 ± 19	96 ± 21	0.782
O_2 saturation	93% ± 4	93% ± 4	94% ± 1	0.474
Blood pressure, mmHg	132 ± 23	134 ± 26	131 ± 26	0.922
	77 ± 18	79 ± 18	79 ± 18	0.851
Treatment with				
Dexamethasone	27 (75%)	19 (83%)	10 (67%)	0.530
Midazolam	19 (53%)	14 (61%)	10 (67%)	0.624
Fentanyl				0.748
-Subcutaneous	4 (11%)	2 (9%)	1 (7%)	
-Endovenous	32 (89%)	21 (91%)	14 (93%)	

opportunities to obtain evidence-based treatment in this field from single-centre randomised placebo-controlled trials are limited by the methodology and ethical problems inherent to studies involving dying cancer patients. One of the major challenges in conducting studies in cancer patients with severe dyspnoea is related to dropout because patients often have a poor prognosis. Therefore, data from appropriate multicentre-powered trials, specially designed for dying patients, are needed. In the meantime, international pharmacovigilance studies may help clarify the efficacy of fentanyl in the management of dyspnoea in frail advanced cancer patients [36, 37].

In summary, this study provides promising results that justify considering intravenous or subcutaneous fentanyl as an option for improving dyspnoea at rest in dying patients. Nevertheless, future studies have yet to clarify the actual benefit of fentanyl in the treatment of breathlessness in dying cancer and non-cancer patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with animals performed by any of the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Human Research Ethics Committee of Hospital Universitario La Candelaria. For this type of study formal consent is not required.

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