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Palliative sedation at the end of life: prevalence, characteristics and possible determinants

Maria Isabel Carrasco-Zafra[1,2], Ricardo Ocaña-Riola[3], Rafael Gómez-García[1,2], Maria Luisa Martín-Roselló[1,2] and Encarnación Blanco-Reina[2,4*]

Abstract

Background Palliative Sedation (PS) at the end of life is practiced and perceived differently by health professionals depending on the geographical location in which they provide their health care. Taking into account this heterogeneity, it is necessary to expand knowledge and provide data on this clinical practice in different contexts and countries. On the other hand, the identification of factors associated with PS could help healthcare professionals, at an early stage, to identify patients more likely to require sedation. The aim of this study was to describe the prevalence and characteristics related to PS in a specialised Palliative Care setting, as well as to analyse factors that could be associated with this procedure.

Methods This was a cross-sectional study including $n=533$ patients who died during the study period in a Palliative Care Unit. Clinical and functional (Barthel and Palliative Performance Scale) variables and the level of complexity were collected. For each patient we assessed whether PS had been performed and, if so, we described the type of sedation, continuity and depth, refractory symptoms, medication used, informed consent and place of death. A multivariate logistic regression model was used to analyse the relationship between several independent variables and PS.

Results The prevalence of PS was 16.7% ($n=82$). Most frequent refractory symptoms were delirium (36.1%), pain (31.9%) and dyspnoea (25%). Factors associated with having a higher odds of PS were having already started treatment with strong opioids (OR = 2.10; 95% CI = 1.16–3.90) and a lower dependency for activities of daily living (OR = 0.41; 95% CI = 0.23–0.70) on admission at PC. Informed consent for sedation was given mainly by representation and only in 19% of cases by the patient himself.

Conclusions Early opioid use and functional status act as factors associated with PS, becoming as clinical evaluations of particular interest during the disease trajectory, which could help to improve individualised care plans for patients at the end of life.

Keywords Palliative sedation, End of life, Palliative care, Refractory symptoms

*Correspondence:
Encarnación Blanco-Reina
eblanco@uma.es
[1]Fundación Cudeca, Málaga 29631, Spain
[2]Instituto de Investigación Biomédica de Málaga IBIMA - Plataforma BIONAND, Málaga 29590, Spain
[3]Escuela Andaluza de Salud Pública, Granada 18011, Spain
[4]Pharmacology and Therapeutics Department, School of Medicine, University of Málaga, Boulevard Louis Pasteur nº32, Málaga 29071, Spain

Background

Correct assessment and treatment by healthcare professionals can usually control patients' symptoms and improve their quality of life [1]. However, in some cases these symptoms cannot be adequately controlled despite intense efforts to identify a tolerable treatment that does not compromise the patient's consciousness, which is defined as "refractory symptom" [2]. In these situations, supervised administration of sedative drugs should be considered as a last resort to alleviate intolerable suffering caused by physical or psychological symptoms that have become refractory [2–3]. This therapeutic procedure is commonly known as "Palliative Sedation" (PS) [2–3]. Although PS remains the most used term, it has become clear that the use of a common term does not guarantee the application of a common concept [4]. With the aim of facilitating the development of clinical practice guidelines (CPG) at an international level, the European Association for Palliative Care (EAPC) prepared a document in which it defined therapeutic (or palliative) sedation as "the monitored use of medications intended to induce a state of decreased or absent awareness (unconsciousness) in order to relieve the burden of otherwise intractable suffering in a manner that is ethically acceptable to the patient, family and health-care providers" [3].

Most CPGs recommend that this procedure be performed seeking the minimum level of sedation that achieves symptomatic control, being proportional and aiming to achieve a level of sedation deep enough to alleviate suffering [3, 5, 6]. PS can be administered intermittently or continuously (until death) and the level of sedation can vary depending on the level necessary to achieve patient comfort [3, 6]. The most frequent indications of PS are delirium, dyspnoea and pain, although their prevalence varies throughout the literature [6–8]. In recent years, other non-physical symptoms such as fear, anxiety and psycho-existential distress are becoming more frequent [8, 9].

According to various systematic reviews, there is great variability in the prevalence of PS, ranging between 12% and 67% [8, 10]. The frequency of this procedure had an even greater variation, ranging from 1.4% in Japan to 80% in the United Kingdom [9]. In another more recent systematic review, which only included prospective studies carried out in palliative care services, PS prevalences between 2% and 28% were confirmed. The practice varies not only across countries but also across clinical settings [11]. Available evidence indicates that the main factors contributing to this wide variability are the management of different PS concepts, diversity in study methodologies, healthcare environments, knowledge and attitudes of doctors, as well as cultural, religious and ethical differences between different settings [6, 12]. Other aspects to consider are the degree of adherence to PS clinical guidelines, level of experience of healthcare professionals and their interpretation of suffering and refractoriness [3]. This represents a central aspect in PS, whose conceptualization has been changing over the last years as new evidence and new ethical-legal frameworks have appeared [6, 9].

PS at the end of life is practiced and perceived differently by health professionals depending on the geographical environment in which they provide their health care. British professionals usually administer low-dose sedatives, with deep sedation being less common in their clinical practice. However, deep sedation is predominantly used in Belgium, highlighting the priority for the professional to respond to the patient's request to alleviate suffering. Moreover, German professionals consider that a formal medical decision based on the patient's desire and the presence of a refractory symptom is essential before starting PS [13]. This heterogeneity in the administration shows that more efforts should be made to move towards a redefinition of the conceptual terms and the PS procedure itself [14].

There are few published studies that have analyzed clinical situations that may have a greater probability of requiring PS. In a recent systematic review and meta-analysis on determinants of PS, 21 studies were included but multivariate analysis was only performed in 11 of the studies. According to their results, in terms of patient-related determinants, the data suggested that younger age, male sex, neoplastic diseases, dyspnea, pain and delirium, as well as those patients who had undergone advance planning of medical decisions, were more likely to receive PS. Regarding the healthcare environment, patients admitted to a hospital were more likely to receive PS compared with those who were at home or in a nursing home [15]. Identification of factors associated with PS could advance care planning at the end of life [16, 17]. In fact, knowing these determining factors can help health professionals to early identify those patients at higher risk of presenting refractory symptoms [15, 16]. We therefore consider that it could be relevant to also analyze the relationship with other elements of interest such as functional status or certain treatments. This information can contribute to the development of comprehensive care plans aimed at minimizing patients' suffering and preserving their dignity [15].

We, therefore, believe it would be pertinent to expand the understanding about the clinical practice of PS by providing data from patients treated in a healthcare environment specialized in PC, focusing particularly on possible factors associated with this clinical procedure. Taking into account that the published works on PS have been performed in very diverse environments and that few include the identification of possible determining factors, currently no Spanish study in the specific context

of palliative care, we consider that further investigation in this particular context is of scientific interest. Our objective was to describe the prevalence and characteristics related to PS, as well as to analyze possible factors associated with its use.

Methods

Design and population

A cross-sectional study with retrospective data collection was performed. The study setting was the Palliative Care Unit (PCU) of the CUDECA Foundation (Málaga, Spain), a hospice integrated into the Andalusian public health system. The resources of this center include an inpatient unit, a day unit and nine home PC teams. Most healthcare is provided at patient homes. This care program provides palliative care through interdisciplinary teams made up of doctors, nurses, psychologists, social workers and physical therapists. Adult patients treated by this PCU who died during a one-year period were included. This is a population-based study as all patients treated and died in this period were included.

Data source and collected variables

The data source consisted of patients' medical records. The variables collected included sociodemographic, clinical (disease, metastasis, symptoms, pharmacological treatments), level of complexity and functional evaluations, all at the time of arrival at the PCU. The level of complexity was assessed using the IDC-Pal© tool, which performs a multidimensional evaluation of the patient and his/her family, and consists of 35 elements, of which 15 reflect a highly complex situation, while 20 represent a complex situation. Depending on the presence or absence of these elements, the situation of each patient is classified as highly complex, complex or not complex [18]. Functional status was assessed using the Barthel scale and the Palliative Performance Scale (PPS). The former includes ten items corresponding to basic activities of daily living (ADLs) (eating, bathing, dressing, grooming, bowel control, bladder control, toilet use, transfer, mobility, stair climbing), and according to the score obtained, describes patient dependence as total (<20 points), severe (20–35), moderate (40–55), slight (>60) or the patient is independent (100). PPS, a modification of the Karnofsky performance scale, is a useful tool to measure progressive physical deterioration, and includes five domains (ambulation, level of activity and evidence of illness, self-care, oral intake and level of consciousness), dividing functional capacity into 11 categories established at 10% decremental levels, from completely ambulatory and in good health (100%) to death (0%).

In line with our main objective, each patient was assessed for whether PS had been performed. Verification of PS indication was based on the clinical record and the definition of "deliberate decrease in the patient's level of consciousness through administration of appropriate drugs with the aim of avoiding intense suffering caused by one or more refractory symptoms", according to the guide of the Spanish Society of Palliative Care (SECPAL) [5]. Cases of PS were only considered when the responsible healthcare professional had registered this procedure explicitly in the medical record. We did not consider cases of PS based only on indirect data (such as the medication used). Doubtful cases in which the professional did not specifically record sedation were classified as missing values with regard to the PS variable. Other related variables of interest were type of sedation (palliative or in the last days or hours of life), its continuity and depth, refractory symptom or symptoms that motivated its indication, sedative medication used, hydration, consent and the moment when it was given, as well as place of death.

Statistical analysis

A descriptive analysis was performed to establish the main population characteristics. Reference data were summarized as numerical data (mean, standard deviation and range) for quantitative variables and as frequency tables for qualitative variables. A multivariate logistic regression model was used to analyze the relationship between independent variables and PS (dependent variable with yes/no categories). To select possible associated factors, basic sociodemographic variables were considered, such as age and sex, presence of the most prevalent symptoms, treatment with opioids, complexity of the situation and patient functional status at arrival to the PCU. These independent variables were based on previous studies [15–17] and on hypotheses considered to be plausible to the research team. The PPS was categorized into scores of below and above 20, a level that reflects a severely impaired functional status. This cut-off point is in line with other similar works [19]. For the Barthel scale, two categories were established: independent patients or patients with slight dependence versus patients with moderate, severe or total dependence.

A p value <0.05 was considered statistically significant. Statistical data analysis was performed using SPSS version 23.0 (IBM SPSS Statistics, Armonk, NY, USA).

Results

General population characteristics

The total population consisted of 533 patients who died during the study period, of whom 16.7% required PS. The mean age was 71.6 years, with no significant differences between sedated and non-sedated patients. Around 60% were men, and although PS was distributed equally between sexes, the frequency of sedation in women was slightly higher (20.5% versus 14.1%; $p=0.06$). 95% of the patients had a caregiver, who in 73% of cases was a

woman, mainly a spouse or child. The major disease was of oncological origin (mostly metastatic disease, 74.5%), and only 6% were non-oncological patients. Regarding the functional status at the beginning of PC, 38.8% of the patients presented a slight dependence, while 13.1% already had a serious dependence for ADLs. Grouping the patients into independent and slight dependence versus moderate, severe and total dependence, sedated patients more frequently had a better functional status at the beginning of their care ($p<0.001$). The majority of the population (71.3%) had a PPS ≥ 50% when arriving at the PCU, and the proportion of better functional status was also higher among patients who were finally sedated compared to those who were not sedated. (82.3% vs. 68.6%, respectively; $p<0.05$). According to the IDC-Pal©, most of the patients were in a highly complex (45.1%), or complex (43.9%) situation. The most prevalent symptoms at the beginning of care and during follow-up by PC were pain, asthenia, constipation and dyspnoea. Regarding the pharmacological treatment prescribed, 79.6% were already receiving some analgesic, with strong opioids being the most used, such as fentanyl (51.4%), morphine (38.2%) and, to a lesser extent, oxycodone-naloxone (7.7%). Death occurred at home in 46% of the study population, although among patients with PS almost all (96.3%) died in the hospital or in the hospice admission unit, while 60% of those who did not receive PS died at home ($p<0.001$). These general characteristics are summarized in Table 1.

Table 1 General characteristics of the population ($N=533$)

Variables	Total ($n=533$)*	No-PS ($n=408$)	PS ($n=82$)
Age, mean (SD)	71.6 (± 12.4)	71.8 (± 12.6)	70.1 (± 11.8)
Sex, n (%)			
Male	319 (59.8)	249 (61.0)	41 (50.0)
Female	214 (40.2)	159 (39.0)	41 (50.0)
Main disease, n (%)			
Oncological	500 (94.0)	384 (94.1)	76 (92.7)
Not oncological	32 (6.0)	24 (5.9)	6 (7.3)
Barthel index, n (%)			
Independent	61 (12.3)	49 (13.0)	7 (9.0)
Slight dependence	192 (38.8)	128 (34.0)	47 (60.3)
Moderate dependence	121 (24.4)	100 (26.6)	11 (14.1)
Severe dependence	65 (13.1)	51 (13.6)	9 (11.5)
Complete dependence	56 (11.3)	48 (12.8)	4 (5.1)
PPS			
≥ 70	126 (24.7)	91 (23.3)	23 (29.1)
50–60	238 (46.6)	177 (45.3)	42 (53.2)
30–40	127 (24.9)	105 (26.9)	13 (16.5)
≤ 20	20 (3.9)	18 (4.6)	1 (1.3)
Level of complexity, n (%)			
Not complex	56 (11.0)	44 (11.3)	6 (7.5)
Complex	224 (43.9)	175 (45.0)	34 (42.5)
Highly complex	230 (45.1)	170 (43.7)	40 (50.0)
Most frequent symptoms, n (%)			
Pain	269 (51.6)	196 (49.0)	49 (61.3)
Asthenia	178 (34.2)	133 (33.0)	30 (37.5)
Constipation	144 (27.6)	115 (28.7)	24 (30.0)
Dyspnoea	113 (21.7)	83 (20.8)	21 (26.3)
Insomnia	100 (19.2)	77 (19.3)	13 (16.3)
Anorexia	72 (13.8)	58 (14.5)	8 (10.0)
Nausea	48 (9.2)	30 (7.5)	14 (17.5)
Depression	37 (7.1)	30 (7.5)	5 (6.3)
Analgesics, n (%)			
Paracetamol	140 (28.5)	104 (27.9)	18 (23.1)
NSAIDs	100 (20.2)	72 (19.2)	23 (29.9)
Metamizole	106 (21.5)	86 (23.0)	13 (16.7)
Weak opioids	41 (8.2)	34 (9.0)	3 (3.8)
Strong opioids	272 (54.6)	191 (50.5)	58 (74.4)
Place of death, n (%)			
Home	244 (46.1)	240 (59.1)	3 (3.7)
Public hospital or CUDECA hospice	285 (53.9)	166 (40.9)	79 (96.3)

PS: Palliative sedation; SD: standard deviation; PPS: Palliative Performance Scale; NSAIDs: nonsteroidal anti-inflammatory drugs

*Missing values (n, percentage) in the total population: PS ($n=43$, 8.1%); Main disease ($n=1$, 0.2%); Barthel Index ($n=38$, 7.1%); PPS ($n=22$, 4.1%); Level of complexity ($n=23$, 4.3%); Most frequent symptoms ($n=12$, 2.3%); Analgesics ($n=35$, 6.6%); Place of death ($n=4$, 0.8%)

Descriptive results on palliative sedation

PS occurred in 16.7% ($n=82$) of the total number of patients included. The average age was 70 years (±11.8; range: 40–95). Only three patients were sedated at home, and the main PS setting was the hospital (68.3%) and the hospice admission unit (28%). Mean time from admission (first contact with CUDECA PC Service) to start of sedation was 103 days (±93) and 122 days (±186) from admission to death.

Regarding type of sedation, it was indicated when patients were in the final days or hours of life in just over half of the sedated patients (56.3%). Death occurred mostly during the first 72 h from the start of sedation, with a mean time of 42.5 h (±39.4) and a median of 33 h. Almost all patients (98%) received continuous sedation and 74.5% deep sedation, although there were missing data for these variables as they were not always clearly recorded in the clinical record. The most frequent refractory symptom was delirium (36.1%), followed by pain (31.9%) and dyspnoea (25%), with two of these symptoms being combined in some patients. In six cases (8.3%) the reason was existential distress. The most common sedative medication was midazolam. Additionally, morphine and scopolamine were used in various combinations. The average number of medications used per patient was 4.3 (±1.9). Parenteral hydration was maintained in 62% of cases. Informed consent for sedation was given mainly by representation (family member, except in one case in which it was given by the attending physician) and only in

Table 2 Palliative sedation characteristics (*N* = 82)

Variable	Value *n* (%)
Setting	
Home	3 (3.7)
Admission (hospital or CUDECA hospice)	79 (96.3)
Type of sedation	
PS	28 (43.7)
PS in last days or hours of life	36 (56.3)
Refractory symptoms	
Agitated delirium	26 (36.1)
Pain	23 (31.9)
Dyspnoea	18 (25.0)
Existential distress	6 (8.3)
Medications used	
Midazolam	51 (82.3)
Morphine	55 (91.7)
Scopolamine	41 (67.2)
Levomepromazine	12 (19.7)
Parenteral hydration	
Yes	33 (62.3)
No	20 (37.7)
Informed consent	
By the patient	13 (19.0)
By legal representative	55 (81.0)
Time when informed consent was given	
Prior to PS	10 (14.7)
At the time of PS	55 (85.3)

PS: Palliative sedation

Missing values (n, percentage) in the PS group: Type of PS (*n* = 18, 22%); Refractory symptoms (*n* = 10, 12.2%); (*n* = 1, 0.2%); Medications used (*n* = 20, 24.4%); Parenteral hydration (*n* = 29, 35.4%); Informed consent (*n* = 14, 17.1%); Time when informed consent was given (*n* = 14, 17.1%)

Table 3 Factors related to palliative sedation. Logistic regression model

Independent variable	OR (95% CI)	*p* value
Age	1.00 (0.98–1.02)	0.805
Sex (male)	0.61 (0.36–1.01)	0.058
Dyspnoea	1.20 (0.65–2.13)	0.535
Pain	1.19 (0.69–2.07)	0.516
Nausea	1.92 (0.91–3.91)	0.075
Depression	0.56 (0.17–1.45)	0.270
Strong opioid treatment	2.10 (1.16–3.90)	0.015
Complex or highly complex situation	1.69 (0.70–4.77)	0.273
Moderate, severe or total dependence (Barthel)	0.41 (0.23–0.70)	0.001
PPS of 20 points of less	0.69 (0.15–2.15)	0.571

OR: odds ratio; CI: Confidence interval; PPS: Palliative Performance Scale

All independent variables correspond to the initial assessment of the patient, when arriving at the Palliative Care Service (at their first contact with palliative care team)

19% of cases by the patient himself, all explicitly verbally. The informed consent was mostly given at the time of the indication (85.3%) and not previously. This information was not always clearly reflected in the medical record, with 15% of data missing for this variable, and was sometimes simply recorded as "the family is informed of the procedure to be performed." The descriptive results on PS are presented in Table 2.

Factors associated with palliative sedation

According to the multivariate analysis performed, the factors associated with PS were having already started treatment with strong opioids and a lower dependence for ADLs (according to the Barthel Index) when starting PC (Table 3).

Age was not shown to be a predictor of sedation. However, in relation to sex, in our population the odds for sedation was 39% lower in men than in women.

None of the most common symptoms was significantly associated with sedation, nor was the level of complexity. However, controlling for the rest of the independent variables in the model (age, sex, functional status, complexity and most frequent symptoms), having already started treatment with strong opioids when arriving at the PCU doubles the odds to perform PS (OR = 2.10; 95% CI = 1.16–3.90).

Regarding initial functional status, a lower dependency was found to be a possible associated factor with PS. Thus, the odds for sedation was 59% lower in patients with dependence (moderate, severe or total) when arriving at the PCU than in those who attended this care while being independent or with slight dependence (OR = 0.41; 95% CI = 0.23–0.70).

Although statistical significance was not reached, the PPS assessment followed the same trend, that is, the worse the functional status (PPS below 20), the lower the odds for PS.

Discussion

The aim of this study was to describe the prevalence and characteristics related to PS in a specialized Palliative Care setting, as well as to analyze factors that could be associated with this procedure. We did not find a very high rate of PS, but it is within the wide international range of available data, and the importance of some specific factors is demonstrated, highlighting the possible role of having strong opioids prescribed early. Most novel is the possible inverse association of initial functional status.

The prevalence of PS was determined as 16.7%, a figure that is within the wide range described in the literature (12–67%) [8, 10]. On a national level, the sedation figures are also similar or somewhat higher to previously reported values ranging from 16 to 54%. That is, the variability already observed in the systematic reviews is replicated in the Spanish studies [20–25]. Compared to our work, in these previous Spanish publications the sample size was smaller and the healthcare environment was

different. As already mentioned, there are several factors involved in the wide variability, ranging from characteristics of the healthcare environment and the medical professionals, to the definition of PS [3, 6, 12, 16, 23]. The fact that there is no uniformity in the concept and terminology of this medical procedure makes comparisons with other studies difficult [26].

Regarding the healthcare framework in which PS is performed, various studies suggest that hospitalized patients are more likely to receive PS than those who are at home or in nursing homes [15, 26–28]. Our data are consistent with this observation, as 96.3% of sedations were performed in a hospital setting (hospital/hospice) and only 3.7% at home, despite the fact that death occurred in the latter location for almost half of the study patients.

The most common type of PS in our population was palliative sedation in the last days or hours of life, defined by SECPAL as "palliative sedation that is used to alleviate intense suffering when the patient is in the last days or hours of life. In this situation, sedation is continuous and as deep as necessary to alleviate said suffering" [5]. That is to say, the patient's clinical data indicate imminent or very near death. This clinical situation is reflected in the new EAPC framework on PS as PS in the final stage of life. Although, consensus on a precise definition of the last stages of life was not reached in this international Delphi process [29]. The Spanish Guide (SECPAL) [5] does not differ in any important point from the EAPC PS framework. In any case, we believe it is important to highlight that this differentiation between PS and PS in the last days or hours of life is a semantic nuance used by the Spanish scientific society, but it does not affect the clinical management of the patients, nor alters the prevalence or statistical analysis of our data. However, it does reaffirm the need to use more consistent terminology on an international level [3]. For this reason, and in agreement with other experts, we agree that work is still ongoing to clarify this concept due to the fact that terminology concerning palliative sedation is heterogeneous and difficult to apply [30].

The indication that most frequently resulted in PS was the presence of delirium, both alone and in combination with other symptoms, followed by pain and dyspnoea. These results are consistent with what was described in previous studies [3, 6–8, 11, 19, 31]. Existential distress was a much less frequent refractory symptom for which PS was indicated, in just 8% of patients. This figure is lower than reported in other studies, in which psychoexistential suffering are described as a reason for PS in up to 24% [21, 23, 31]. Data from a recent systematic review are consistent with the aforementioned findings, demonstrating that between 10 and 24% of sedations were performed due to psychological or existential distress [11].

Regarding the treatment used, midazolam was the most widely used sedative, which is recommended as first-line treatment by the SECPAL and the EAPC [3, 5]. This finding coincides with the majority of previous studies [7, 9, 19, 23, 31]. Morphine was also administered during PS in most patients. However, these data must be interpreted with caution, as prior initiation of treatment with morphine is common to control symptoms such as pain and dyspnea, and its use must subsequently be maintained in order to ensure symptomatic control [6, 31]. Therefore, the prescription of morphine at the time of PS is not always to provide a sedative action, but rather a part of a prior necessary treatment.

Regarding other aspects of the PS process, informed consent was primarily given by patient family members. In our opinion, this could be partly related to the patient being less aware of the prognosis than the family, which seems to reflect certain behaviors rooted in sociocultural-based beliefs or customs. In fact, in Spain, and other countries with a Mediterranean culture, it is still common for patients to be poorly informed and/or unaware of their prognosis [31]. That the consent for sedation was given mostly by representation also coincides with what was found in other studies from southern Europe [22, 31]. Although active participation of the patient is ideal, it should be highlighted that on many occasions we are faced with situations that involve altered cognitive capacity, great clinical fragility and high emotional impact, which limits a patient's competence to give informed consent.

Analyzing possible factors associated with PS, we did not find age to be a predictor of PS, while female sex, although it did not reach statistical significance, demonstrated a tendency to have a greater odds for sedation. Although the literature offers diverse results [17], a significant number of studies have detected a higher proportion of sedations in males [15, 16, 27]. None of the most frequent symptoms in our patients was significantly associated with PS, although there are studies that have found potential associations with pain, dyspnoea and delirium [15]. This diversity of results is consistent with the variety and complexity of variables associated with PS described in a recent meta-analysis [15]. The only Spanish study included in said review was not performed in a specific Palliative Care context and the profile of its patients is not comparable to that of our work. This study was a retrospective multicenter study that exclusively included patients who died in Internal Medicine Units and the results demonstrated that having a terminal illness and length of hospital stay were independently associated with the use of palliative sedation [25].

We have verified that having already started strong opioid treatment doubles the odds to perform PS. There are few studies that have analyzed possible PS predictors in

depth and with multivariate models, and in even fewer studies that have included the use of opioids as an independent variable. One of these studies demonstrated a significant association between continuous PS and the use of opioids at admission (OR 1.90; 95% CI 1. 18−3.05) [16]. This association, and in a dose-dependent manner, was also found in another work [32]. In our opinion, the association between PS and the use of strong opioids could indicate that when certain symptoms, such as pain or dyspnoea, already require the use of these drugs when arriving to the PCU, they are probably more difficult to control during the rest of the disease trajectory, becoming refractory in a considerable percentage of patients. Perhaps the presence of delirium induced on many occasions by the use of these drugs could also influence this association [32, 33].

On the other hand, the odds ratio for sedation was 2.44 for those patients who are independent or with slight dependence when arriving at the PCU, compared to those who already present dependence (moderate, severe or total) at the time of PCU referral. For a better understanding of this finding, it is important to note that the odds ratio found corresponds to the initial assessment of the Barthel Index and not to the moment in which PS was indicated, a state in which the patient already had a worse functional state. Although statistical significance was not reached, the PPS assessment follows the same trend, that is, the worse the functional status (PPS below 20), the lower the odds for PS. There are few studies that have assessed this relationship, except for a multicenter study in which a possible association between sedation and better functional status was found [16].

This study has limitations. Collecting data from a single healthcare setting may reduce external validity of the results. However, we believe that the patients included in this study are representative of patients in general with advanced disease treated by PCUs. In fact, characteristics such as sociodemographic, type of disease and symptoms are comparable with those of other published studies [20, 21, 23]. Regarding the Spanish health landscape, we would like to point out that a substantial proportion of the health care in Palliative Care is performed in the patient's home [34], a relevant fact which coincides with our palliative care unit (most home PC teams) and that advocates more in favor of similarities than differences with the rest of the country. At this level our setting could be considered representative. On the other hand, the cross-sectional design does not allow us to establish causal relationships, but it does allow detection of some factors that could be related to the indication for PS. By considering as an undoubted criterion of sedation that this procedure was explicitly described by the professional in the medical record, without considering cases based only on indirect data, we may have underestimated the prevalence of PS due to not including possible cases for which the procedure was not registered. Finally, the retrospective nature of the study means that the information collected depends on the quality of the data included in the medical records. Here we must point out that 8.1% of values for the main variable were missing, that is, whether or not PS was indicated. This may be related mainly to two circumstances. Firstly, the poor registration in some cases of the medical records, perhaps more frequently in certain hospital areas where some deaths occurred and, secondly, a certain resistance to clearly label the decision to indicate PS, in many cases using euphemisms such as "comfort measures are initiated" or others. That there is room for improvement for information recorded in medical records is something shared with other authors [22, 25, 26]. This recording problem would be greatly alleviated with a prospective study design and with greater awareness among professionals about the importance of reflecting all clinical data and decision-makings of interest in the medical record.

This research also has strengths, such as having collected a substantial and diverse set of clinical and functional data that support the analysis performed, providing results and evidence in a priority research area. We also want to highlight the performance of a multivariate statistical approach, recommended in a recent review due to the scarcity of publications with this type of analysis [15].

In our opinion, these types of studies deepen the understanding of characteristics of a procedure of special clinical interest, and help to identify clinical aspects or conditions that may be predictive of PS. This allows the development of individualized and comprehensive care plans, aimed at optimal care at the end of life.

Conclusions

In this work we conclude that early use of opioids and functional status are factors associated with PS, and can be considered as assessments of special interest during the disease trajectory.

Abbreviations

PC	Palliative Care
PS	Palliative Sedation
EAPC	European Association for Palliative Care
PCU	Palliative Care Unit
ADLs	Activities of Daily Living
PPS	Palliative Performance Scale
SECPAL	Spanish Society of Palliative Care

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Author contributions

E.B.-R. and M.I.C.-Z. conceptualized and designed the study. R.O.-R. provided methodological support. M.I.C.-Z. and R.G.-G. contributed to acquisition of data. M.L.M.-R. and R.G.-G. provide clinical expertise in study conduct. E.B.-R. and R.O.-R. analysed the database. M.I.C.-Z. and E.B.-R. interpreted the results and wrote the manuscript. All authors read, reviewed, provided feedback and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The present study was approved by the IRB Málaga Provincial Clinical Research Ethics Committee (project code EBR-SED-2017-1). Given the retrospective nature of the study and the adequate dissociation of the deceased patients' personal data, the need for consent to participate was waived by this Ethics Committee. This decision was based on national regulations (Royal decree 957/2020 and Personal data protection Law 3/2018). The provisions of the Declaration of Helsinki, revised in 2013, regarding ethical principles for research on human beings, were fully complied with throughout this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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