Palliative sedation in patients hospitalized in internal medicine departments.

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Declaration of authorship

Jesús Díez-Manglano and Soledad Isasi de Isasmendi Pérez designed the study and performed data collection and analysys. Rosa García Fenoll performed data analysys. Luis Ángel Sánchez, Françesc Formiga, Vicente Giner Galvañ, Carlos Dueñas, Bernardino Roca Villanueva, Cristina Estrada Díaz, Emilio Casariego Vales performed data collection. The manuscript was drafted by J. Díez-

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ABSTRACT

Context: Palliative sedation is used to relieve end-of-life refractory symptoms.

Objective: To describe the use of palliative sedation in patients who die in internal medicine departments.

Methods: An observational, cross-sectional, retrospective and multicenter, clinical audit study was conducted in 145 hospitals in Spain and Argentina. Each hospital included the first 10 patients who died in the internal medicine department, starting on December 1, 2015.

Results: We included 1447 patients, and palliative sedation was administered to 701 (48.4%). Having a terminal illness (OR 2.469, 95%CI 1.971-3.093, p<0.001) and the length of the hospital stay (OR 1.011, 95%CI 1.002-1.021, p=0.017) were independently associated with the use of palliative sedation. Consent was granted by the families of 582 (83%) patients. The most common refractory symptom was dyspnea, and the most commonly used drugs for sedation were midazolam (77%) and morphine (89.7%). An induction dose was administered in 25.7% of the patients. Rescue doses were scheduled for 70% of the patients, and hydration was maintained in 49.5%. Pain was more common in patients with cancer, while dyspnea was more common in those without cancer. Rescue doses were employed more often for the patients with cancer (77.8% vs. 67.7%, p=0.015). Monitoring the palliative sedation with a scale was more frequent in the patients with cancer (23.7% vs. 14.3%, p=0.008).

Conclusions: Palliative sedation is employed more often for terminal patients. There are differences in the administration of palliative sedation between patients with and without cancer.

KEY MESSAGE

This multicenter observation study describes the use of palliative sedation in patients who die in internal medicine departments. The most common refractory symptom was pain in patients with cancer and dyspnea in those without cancer. Rescue doses were employed more often for patients with cancer.

KEYWORDS

Palliative sedation; Terminal care; Internal medicine; Palliative care.

RUNNING TITLE

Palliative sedation in hospitalized patients

INTRODUCTION

In industrialized countries, approximately 50% of deaths currently occur in hospitals [1,2]. When the end of life approaches, patients (by their own will or that of their relatives) often visit hospitals for relief or for greater comfort in their last moments of life. This social demand has impelled the promulgation of laws on dignity in end-of-life care [3-5].

Advanced and terminal disease often causes intense and difficult-to-control symptoms that need to be alleviated. To achieve this, palliative sedation (PS) is sometimes necessary. PS is defined as the deliberate reduction of the patient's level of consciousness to relieve the intense suffering caused by one or more refractory symptoms [6,7].

The European and American palliative care associations recommend auditing PS practices [8,9]. In Spain, up to 6 of every 10 patients who die in a hospital do so in internal medicine departments [10]. Although several studies have been conducted on the administration of PS in Spain, the studies have been limited to a single hospital or to palliative care units [11,12]. Worldwide, research on deep continuous palliative sedation maintained until death outside intensive care units, and especially in internal medicine departments, is scarce.

The aim of this study was to report the practices and circumstances of administering PS to patients who eventually died in internal medicine departments in Spain and Argentine.

MATERIAL AND METHODS

Design

The Last Days of Life in Internal Medicine (*Últimos Días de Vida en Medicina Interna*, UDVIMI) study has been previously described [13], and was an observational, cross-sectional, retrospective multicenter study in which 145 public and private hospitals, 143 in Spain and two in Argentina participated. The investigators in each hospital included the first 10 patients who died in the internal medicine department, starting on December 1, 2015.

Data

The investigators reviewed the patients´ history. For each patient they collected the following data in a chart review: age, sex, institutionalization, emergency department care and hospitalizations in the previous year, the presence of polypathology, Barthel index before the hospitalization, number of drugs typically taken before the hospitalization, terminal illness at admission, whether death was expected in the next days after admission, patient's understanding of their vital prognosis, their ability to make decisions, whether advance directives or previous decisions had been made, symptoms of advanced disease during hospitalization, length of hospitalization at the time of death and the use of PS. Polypathology

was defined according to the regional government of Andalusia, i.e. the presence of two or more chronic and symptomatic diseases with frequent re-exacerbations that have a negative effect on the functional situation and generate requirements in the various levels of sanitary attention [14]. Terminal illness was defined with the criteria of the National Hospice Organization [15]. Anorexia, pressure ulcers, bed-ridden, dyspnea at rest, cachexia, pain, delirium and dysphagia were considered symptoms of advanced disease. PS was defined as the use of sedative drugs to reduce the level of consciousness of the patient and to alleviate refractory symptoms previously to death, i.e. continuous deep sedation [7,16].

For the patients who were administered PS, data were also collected on the refractory symptoms that motivated the sedation, the request for informed consent, the individual(s) who gave this consent, the drugs and doses employed in the PS, the use of induction and rescue doses, hydration maintenance, use of a scale to monitor the PS, the practitioner who indicated the PS and the prior discussion by the therapeutic team for the PS decision. Usually, the therapeutic team consists mainly of physicians and nurses. They discuss and finally share and make the decision. Occasionally, other professionals such as social workers or psychologists participate.

The study was conducted in accordance with the Spanish law on the protection of personal data and was approved by the Clinical Research Ethics Committee of Aragon (PI 15/0322).

Statistical analysis

The qualitative variables are presented as n (%) and were compared with the chi-squared test. The quantitative variables are presented as mean (standard deviation) and were compared with Student's t-test.

To determine the factors associated with PS, we constructed a logistic regression model. In the multivariate analysis, we employed the stepwise forward technique including all variables with statistical significance ($p<0.1$) in the univariate analysis.

In all cases, the level of statistical significance was $p<0.05$. All calculations were performed with the Statistical Package for Social Sciences (SPSS) (version 22.0, SPSS Inc., Chicago, IL).

RESULTS

Eighty-two general hospitals and 63 other hospitals, including 57 county, 5 long-term care, and 1 military hospitals, participated in this study.

Patient characteristics

We included 1447 patients with a mean age of 82.5 (10.4) years, 699 (48.3%) of whom were women. The patient characteristics are presented in **Table 1**. PS was administered to 701 (48.4%) patients.

The patients who were administered PS were more often considered to have a terminal illness at admission and had been hospitalized less frequently in the last year. At admission, death was expected more frequently for the patients who were administered PS (69.6% vs. 56.6%, p<0.001). The prevalence of anorexia, dysphagia and cachexia and the total number of terminal illness symptoms were higher in the patients who died without PS. The patients with PS had a longer stay than those who died without PS (11.9 vs. 9.6 days, p=0.002).

Administration and technique of palliative sedation

A regression logistic analysis was performed with data from 1404 patients. **Table 2** shows the factors independently associated with dying under PS. Being hospitalized the previous year (OR 0.757, 95% CI 0.607-0.943, p=0.013) and presenting anorexia (OR 0.726, 95% CI 0.552-0.953, p=0.021) or cachexia (OR 0.697, 95% CI 0.518-0.938, p=0.017) were associated with a lower use of PS. Being considered a patient with a terminal illness (OR 2.469, 95% CI 1.971-3.093, p<0.001) and a longer hospital stay were associated with a higher use (OR 1.011, 95% CI 1.002-1.021, p=0.017).

PS was indicated by the patient's attending physician in 513 (73.2%) of the cases and by the on-call physician in 178 (25.4%) cases. In 10 (1.4%) patients the palliative sedation was performed by a palliative consultant physician. The decision to administer PS was reached by agreement of the therapeutic team, physicians and nurses, in 473 (67.5%) of the cases. Consultation with the Ethics Committee was necessary for only 5 (0.7%) patients.

A request for informed consent for the PS was recorded in the medical history of 473 (67.5%) of the patients. A written consent document was signed in only 34 (4.9%) cases. Consent was granted by the patient in 25 (3.6%) cases and by their relatives or close friends in 582 (83%) cases. For 94 (13.4%) cases, the source of consent was not known.

The refractory symptoms that motivated the administration of PS were dyspnea (520 patients, 74.2%), pain (215, 30.7%), psychological suffering (168, 24%) and delirium (161, 23%). The mean number of refractory symptoms was 1.6 (0.7), and 47.5% of the patients presented more than one symptom.

The most often used palliative drug was midazolam (540, 77.0% of patients), but also, other benzodiacepines, propofol, levomepromazine and chlorpromazine were used. Other concomitant not sedative drugs as morphine (629, 89.7% of patients), butylscopolamine (267 patients, 38.1%) and haloperidol (158, 22.5%) were also frequently administered. Other drugs occasionally employed included metoclopramide, ondansetron, hyoscine, diazepam, quetiapine and corticosteroids. An induction dose was administered to 25.7% of the patients, while rescue doses were scheduled for 70% of the patients. Hydration was maintained in 49.5% of the patients, and the PS intensity was monitored with a validated scale in 16.8% of the cases. The median (interquartile range) of time from the start of PS to death was 2 (1-3) days.

Patients with and without cancer

Table 3 shows the characteristics of the patients with and without cancer who were administered PS. The patients with cancer more often had refractory pain, and the patients without cancer more often had refractory dyspnea. The patients with cancer more often presented more than one refractory symptom (58.6% vs. 43.5%, p=<0.001). The patients with cancer were more often sufficiently capable of making decisions, knew their prognosis and granted their consent for PS (all p<0.001).

There was no difference in the use of induction doses, but he patients with cancer were more frequently administered rescue doses (77.8% vs. 67.7%, p=0.015). PS was monitored with scales more frequently in the patients with cancer.

Terminal patients

At admission, 751 (51.9%) patients were considered to be terminal. In 237 (31.6%) of the terminal patients, the disease was cancer. Terminally-ill non-cancer diseases were neurologic, mainly dementia, in 40.7% of patients, cardiac (21.9%), respiratory (20.3%), renal (9.3%), infectious (5.3%) and hepatic (1.5%) One hundred seventy five patients (23.8%) had more than one terminal disease. PS was administered to 148 (62.4%) terminal patients with cancer and to 274 (55.0%) patients without cancer (p=0.057).

The time from admission to the start of PS was longer for the terminal patients with cancer (8.6 vs. 6.3 days, p=0.043). The same was true for the time from

admission to death. The terminal patients with cancer were more frequently administered induction doses of PS (32.4% vs. 24.5%, p=0.031) and rescue doses (77.7% vs. 68.2%, p=0.005).

DISCUSSION

Our study's main findings were that PS for patients who die in internal medicine departments is administered more often to patients already identified as in terminal condition at hospital admission. We also found differences in the application of PS between patients with cancer and those with other diseases.

The National Hospice and Palliative Care Organization considers PS an option that should be considered by health professionals, patients and relatives to prevent the intractable and intolerable suffering of patients whose death is imminent [9]. In accordance with this consideration, PS was administered in our study more to patients with a terminal illness and in those who, when admitted, were expected to die. A previous study observed that establishing the patient's terminal condition in the medical history determined the subsequent decision making, including the prescription of PS, the withdrawal of medication and the use of do-not-resuscitate orders [17].

The rate at which PS is employed varies significantly, depending on whether it is administered at home or in the hospital and in palliative care units or in other hospital departments [18]. In the various studies published in the past 5 years, the prescription of PS has ranged from 21% to 63% of patients who died [19-21]. In our study, almost half of the patients who died were sedated. The prevalence of use of PS is increasing, because nowadays to alleviate suffering previous to death is a cornerstone of the health care. However, it is important to note that the objective of PS is to eliminate the symptoms refractory to other treatments, and its administration must not be indiscriminate. Dyspnea and delirium are typically the refractory symptoms that most often lead to the prescription of PS [19-27].

In a national study performed in palliative care units in Austria, PS was administered more frequently to patients with cancer [27], with a similar trend observed in a study in the Netherlands [28]. We found a similar but not statistically significant tendency. A surprising finding of our study was that the presence of anorexia and cachexia was associated with a lower use of PS. It appears that not eating and being extremely thin were associated with imminent death and that PS was deemed unnecessary. However, we do not have a persuasive explanation for this finding given the study's retrospective nature, which does not allow us to establish the causality.

The laws state that patients (or their representatives if the patient is incapacitated) have the right to know the prognosis of their disease, to make the decisions on their care process and grant their consent before care is administered [3-5].

Additionally, this entire process must be recorded in the medical history, all of which is applicable to PS. In our study, only 1 of every 5 sedated patients knew their prognosis, and only 1 of every 3 were competent to make decisions. The decision for PS was therefore made mostly by relatives and close friends together with physicians. However, the fact that informed consent had been requested was recorded explicitly in the medical history in only 2 of every 3 cases. Other previous studies have already observed that there is room for improvement in the information regarding PS that is recorded in the medical history [29,30].

PS should be started jointly by a physician and a nurse, preferably those with experience in caring for patients at the end of life [8]. It is important that physicians who regularly treat the patient participate in the patient/relative information process and in the indication for starting PS. In our study, PS was started by the on-call physician for one quarter of the patients. This is a positive finding because clinicians need to act promptly when symptoms become refractory, without waiting for the regular physician, which can cause delays of hours or days in the case of night and weekend shifts. Continuity of care needs to be ensured in end-of-life situations, and the regimens agreed upon with the patient or their relatives need to be recorded in the medical history.

Midazolam is the drug recommended in clinical practice guidelines for PS [8]. In our study, as with most previously published studies, midazolam was the most commonly employed drug [19-21,25,27]. Nevertheless, in a Chinese study, diazepam was employed preferentially [26]. Other nonsedative drugs such as

morphine and butylscopolamine were also frequently employed for our patients. Morphine, although not a drug for PS, should be maintained when it has previously been used as an analgesic. Likewise, adding scopolamine is recommended to prevent the onset of rales or to decrease their intensity. An initial dose of midazolam is usually necessary to induce PS. Maintenance doses should then be administered, preferentially in a continuous infusion. If the sedation is insufficient, the dose should be increased, or rescue doses should be administered. In a study published in Spain in 2016, induction doses were employed for 10% of the patients, and rescue doses were employed for 38% [30]. In our study, the administration of induction and rescue doses was 2-fold higher. To monitor the PS, the recommendation is to use scales, such as the Richmond scale and the Ramsay scale [31,33]. The use of these scales helps standardize the intensity of the PS and avoid subjective assessments.

In terminal patients, the time from the start of PS to death varies and depends on whether hydration and intravenous nutrition are maintained. In most studies, this period varies between 1 and 3 days, a duration similar to what we observed [22-27]. The practice and opinions regarding the maintenance of hydration and artificial nutrition vary and are related to the attitudes of the patients, their relatives and the clinicians involved in the PS, as well as the local uses and practices [7]. However, it should be noted that studies that have compared the survival time of sedated and nonsedated terminal patients have found no differences [33,35]. This is an important finding and should be clearly explained to the patients' relatives, who are frequently distressed and have concerns about this aspect of PS [35].

An important finding is that there are differences in the administration of PS to patients with or without cancer. Although dyspnea was the most common refractory symptom in both patient groups, the patients with cancer had more pain, while the patients without cancer had more dyspnea. Swart et al, in a national survey in the Netherlands, reported the same findings [36]. We observed that the induction and rescue doses were administered more frequently to the patients with cancer. We do not have an explanation for these findings, but it is possible that, when deciding to administer PS, clinicians and relatives assign greater value to relieving pain than to relieving dyspnea. In addition, international variations in clinical practice guidelines has been reported, and the adherence to this guidelines is low [37,38].

Our study had several limitations. Firstly, this was a retrospective study. However, in studies on end-of-life care, this retrospective design has advantages given that it easily identifies the study cohort and enables the inclusion of all patients and not just a random sample. Indicators to assess the performance of care (in this case, for PS) can thereby be developed quickly. Secondly, all data were collected from medical records. We cannot therefore rule out an under-recording of various aspects of the practice of PS that were employed but not recorded. Thirdly, in all of the hospitals, 10 cases of patients who died were recorded without considering the number of beds or admissions. It is possible that the weight of the data of some hospitals could be underestimated or overestimated, although the wide representation of hospitals from all levels minimizes this limitation.

In conclusion, PS is applied more often to patients identified as in their final stage of life at the time of hospital admission. Additionally, there are differences in the administration of PS to patients with and without cancer. We need to establish protocols and standards of good clinical practice on PS for patients with terminal non-neoplastic illness.

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The authors declare that there is no conflict of interest

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Table 1. Characteristics of the Patients Included in the Study				
	Total (n=1447)	Palliative sedation (n=701)	No palliative sedation (n=746)	p
Age*	82.5 (10.4)	82.9 (10.4)	82.2 (10.4)	0.148
Female sex	699 (48.3)	334 (47.6)	365 (48.9)	0.626
Private hospital	218 (15.1)	109 (15.5)	109 (14.6)	0.618
Institutionalized	343 (23.7)	167 (23.8)	176 (23.6)	0.706
Polypathological patient¥	1065 (74.3)	520 (75.0)	545 (73.6)	0.548
Treated in the emergency department without hospitalization in the last year§	710 (52.9)	330 (51.2)	380 (54.5)	0.218
Admitted to hospital in the last year£	788 (56.1)	356 (52.8)	732 (59.2)	0.016
Functionality (Barthel index)*	41 (34)	42 (34)	41 (34)	0.462
Typically consumed drugs*	7.9 (3.8)	7.8 (3.8)	8.0 (3.8)	0.308
Death expected at admission	910 (62.9)	488 (69.6)	422 (56.6)	<0.001
Patient is considered terminal at admission#	751 (51.9)	431 (61.5)	320 (42.9)	<0.001
Terminal illness symptoms#	1263 (88.5)	608 (88.2)	655 (88.8)	0.763
Anorexia	499 (35.0)	210 (30.5)	289 (39.2)	0.001
Pressure ulcers	196 (13.7)	104 (15.1)	92 (12.5)	0.150
Bed-ridden	609 (42.7)	286 (41.5)	323 (43.8)	0.389
Dyspnea at rest	671 (47.0)	326 (47.3)	345 (46.7)	0.830
Cachexia	273 (19.1)	107 (15.5)	166 (22.5)	0.001
Pain	404 (28.3)	189 (27.4)	215 (29.1)	0.476
Delirium	291 (20.4)	128 (18.6)	163 (22.1)	0.100
Dysphagia	280 (19.6)	119 (17.3)	161 (21.8)	0.031
No. of symptoms*	2.2 (1.5)	2.1 (1.5)	2.3 (1.5)	0.002
Length of hospital stay until death*	10.7 (14.2)	11.9 (15.6))	9.6 (12.6)	0.002
The data are presented as frequency (percentage) or *mean (standard deviation) ¥ data from 1433 patients, § data from 1342 patients, £ data from 1404 patients, # data from 1427 patients				

Table 2. Factors Associated with Administering Palliative Sedation				
	Univariate		Multivariate	
Variable	OR (95% CI)	p	OR (95% CI)	p
Hospitalization in the previous year	0.772 (0.625-0.954)	0.017	0.757 (0.607-0.943)	0.013
Anorexia	0.681 (0.547-0.848)	0.001	0.726 (0.552-0.953)	0.021
Cachexia	0.634 (0.484-0.829)	0.001	0.697 (0.518-0.938)	0.017
Dysphagia	0.748 (0.575-0.974)	0.031		
Terminal illness	2.125 (1.722-2.622)	<0.001	2.469 (1.971-3.093)	<0.001
No. of terminal symptoms	0.897 (0.838-0.960)	0.002		
Time to death, days	1.012 (1.004-1.021)	0.003	1.011 (1.002-1.021)	0.017
Abbreviations: CI, confidence interval; OR, odds ratio.				

Table 3. Palliative Sedation in Patients with and without Cancer				
	Total (N=698)	Patient with cancer (n=194)	Patient without cancer (n=504)	p
Patient was competent for making decisions	133 (19.1)	89 (45.9)	44 (8.7)	<0.001
Patient knows their situation and vital prognosis	97 (13.9)	70 (36.1)	27 (9.4)	<0.001
Physician who indicated the PS				
Regular	511 (73.2)	145 (74.7)	366 (72.6)	0.575
Shift	178 (25.5)	44 (22.7)	134 (26.6)	0.290
Consent				
Requested	470 (67.3)	127 (65.5)	343 (68.1)	0.512
Signed document	34 (4.9)	13 (6.7)	21 (4.2)	0.170
Granted by patient	25 (3.6)	16 (8.2)	9 (1.8)	<0.001
Refractory symptoms				
Dyspnea	517 (74.3)	113 (58.2)	404 (80.5)	<0.001
Pain	215 (30.9)	107 (55.2)	108 (21.5)	<0.001
Delirium	161 (23.1)	54 (27.8)	107 (21.3)	0.067
More than one symptom	329 (47,7)	112 (58.6)	217 (43.5)	<0.001
Time to start of PS*, days	9.5 (14.5)	10.1 (14.4)	9.3 (14.6)	0.513
Days from admission to death*	11.9 (15.6)	12.5 (14.7)	11.7 (16.0)	0.525
Induction dose	179 (25.6)	57 (29.4)	122 (24.2)	0.112
Rescue dose	488 (69.9)	147 (75.8)	341 (67.7)	0.015
Hydration	346 (49.6)	104 (53.6)	242 (48.0)	0.299
Monitoring with validated scale	118 (16.9)	46 (23.7)	72 (14.3)	0.008
The data are presented as frequency (percentage) or *mean (standard deviation) Abbreviation: PS, palliative sedation.				