Original Article

Palliative Sedation in Patients With Advanced Cancer Followed at Home: A Prospective Study

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Abstract

Context. Home care programs in Italy.

Objectives. The aim of this study was to assess a protocol for palliative sedation (PS) performed at home.

Methods. A total of 219 patients were prospectively assessed to evaluate a PS protocol in patients with advanced cancer followed at home by two home care programs with different territorial facilities. The protocol was based on stepwise administration of midazolam.

Results. A total of 176 of the patients died at home, and PS was performed in 24 of these patients (13.6%). Younger patients received the procedure more frequently than older patients ($P = 0.012$). The principal reasons to start PS were agitated delirium ($n = 20$) and dyspnea ($n = 4$). Mean duration of PS was 42.2 ± 30.4 hours, and the mean doses of midazolam were 23–58 mg/day. Both the home care team and the patients' relatives expressed optimal or good levels of satisfaction with the procedure in all but one case, respectively.

Conclusion. This protocol for PS was feasible and effective in minimizing distress for a subgroup of patients who died at home. The characteristics of patients who may be effectively sedated at home should be better explored in future studies. J Pain Symptom Manage 2014;47:860–866.

Key Words

Palliative sedation, end of life, palliative care, midazolam

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Introduction

Some terminally ill patients near the end of life may experience intolerable suffering refractory to targeted palliative therapies. As death approaches, symptom control may become more difficult and the goal of a peaceful death may be unsuccessful. Palliative sedation (PS) is considered to be an effective treatment modality for dispelling refractory symptoms when aggressive efforts fail to provide relief in terminally ill patients with cancer.[1,2] According to the definition proposed by the European Association for Palliative Care, PS is the use of sedative medication to relieve intolerable suffering in the last days of life.[3] An even more specific definition is the use of nonopioid drugs to control refractory symptoms in the dying. This palliative practice has been used for years, with a variable incidence ranging from 2% to 52%,[4] depending on the setting, population, cultural, ethnic and religious factors, institutional policies, or national legislation rather than on appropriate and timely decision making based on real patients' needs.

Patients with cancer spend most of their time at home, particularly in the last weeks of life.[5] Admission to hospital or staying at home in last days of life depends on many different factors, including resource availability and personal preference, other than clinical needs.

PS can be performed at home. In a systematic review, the frequency of PS at home was variable (13–35%), confirming data observed in a previous survey of patient assessment in the last days of life.[6] In a previous retrospective analysis of home care patients with cancer who died at home, the frequency of PS was 13.2%.[7] However, much information, including indications, mean duration, and drug used for PS, was not available from the literature or clearly structured, or no a priori definition of PS was adopted.[8] The large variability observed in the use of PS among centers suggests a lack of appropriate criteria adopted for the definition of PS.

The Home Care—Italy (HOCAI) group was established with the intent of disseminating and implementing the information gathered on patients with cancer followed at home, given the paucity of existing data in this setting. The aim of this study was to assess the efficacy of a PS protocol, established by the HOCAI group in a preliminary investigator meeting, in a prospective study of patients with advanced cancer followed at home. Secondary aims included analysis of the characteristics of these patients between two centers with different territorial facilities, any problems encountered by the teams, and level of satisfaction of the team and relatives.

Methods

The study was conducted in two home palliative care units (HPCUs) of the HOCAI group that adhered to the protocol. The activities of these units have been described elsewhere.[6–8] The two HPCUs provide similar levels of assistance, with visits ranging between two and three a week for physicians, and three and seven a week for nurses, in addition to providing on-call visits in case of need.[6] Treatments are based on local protocols aimed at controlling psychological and physical symptoms. Physicians, nurses, psychologists, physiotherapists, and social workers are members of the multidisciplinary team, coordinated by a central agency. Cases are discussed in a weekly meeting or more often when necessary, with medical supervision. The teams receive continuous education and have more than 5 years' experience in home palliative care.

One of the teams participating in this study is from L'Aquila, a mountain community with one hospital with an acute oncology unit and a palliative care service connected to a home care program, providing continuity of care after discharge with the same health personnel. The other is from Turin, a metropolitan area with many oncology units and various palliative care services. The largest palliative care service, FARO (Association for Assistance and Research in Oncology), provides home care and offers hospice admission. Patients are referred by different oncology units and then can be followed at home or in hospice, according to clinical and social needs.

The PS Protocol

The PS protocol was developed after some preliminary meetings of HOCAI members and updated after a series of conference calls,

to find the best compromise between the local policies of each institution and supervision of the group leader. All the patients who were admitted to the HPCUs in a six month period, from July 2012 through December 2012, were assessed. Patients who died at home during this period were included in the study. Informed consent (by relatives) and ethics committee approval were obtained.

All the patients who were administered "specific sedatives to relieve intolerable suffering from refractory symptoms by reducing a patient's level of consciousness with nonopioid sedative medication in the last days of life" were selected and considered as patients receiving PS, according to a definition shared in a preliminary investigator meeting and adopted in a previous retrospective study.[7] The characteristics of this group of patients were recorded on a structured sheet, as well as the indication to start PS. Information regarding who proposed the start of PS was recorded, and whether the patient or relatives were involved in the decision and if there were doubts or internal conflicts. Reasons for discontinuation of PS also were recorded.

After the decision to start PS was shared with relatives, intravenous or subcutaneous midazolam was started in doses of 20–30 mg/day, independent from the previous use of sedative or neuroleptic drugs. Opioids were maintained, if previously given for other reasons (pain or dyspnea), via nonoral routes, with no intention to sedate. If the physician judged it appropriate, the second step was started, increasing the dose of midazolam up to 30–60 mg/day. The third step was to use doses higher than 60 mg/day. Other sedative drugs, including neuroleptics, were allowed with the third step, or continued if used before, and dosages were used flexibly according to the patients' needs. Symptomatic agents, commonly used in the last days of life (e.g., diuretics and antisecretory agents), were administered when necessary. Drugs and doses were changed according to clinical need, with no strict protocol.

Assessment

Pain, dyspnea, agitated delirium, and psychological distress data, rated on a zero to 10 numerical scale, were collected at the beginning of PS (T0) and then at one day intervals until death (T1, T2, T3, and so on). Information about drugs and doses used during PS was recorded at the same times. Relatives were asked about symptom intensity when the patients were unable to provide this information. The Communication Capacity Scale and the Agitation Distress Scale also were used to monitor the level and efficacy of PS.[9] Finally, the level of satisfaction regarding the efficacy of PS for home physicians and relatives (optimal, good, fair, or poor) was recorded, when available, within one week after the patient's death.

Statistical Analysis

Data were collected and analyzed using SPSS Software v. 14.0 (SPSS, Inc., Chicago, IL). Descriptive summaries for all measures are reported as means and standard deviations for numeric variables, and as percentages for categorical variables. Statistical analysis of quantitative data, including descriptive statistics, was performed for all the items. The Chi-squared test was used to make comparisons with respect to categorical variables, and Fisher's exact test was used if sample size criteria were not met for Chi-squared approximation. One-way analysis of variance was used for parametric analysis. All *P*-values were two sided, and *P*-values less than 0.05 were considered statistically significant.

Results

A total of 219 patients were surveyed during the study period, 117 and 102 in L'Aquila and Turin, respectively. Mean age was 73.6 ± 13 years, and 112 patients (51.1%) were male. The mean Karnofsky Performance Status score at the time of home care admission was 57.5 ± 18.7. Primary cancer diagnoses were, in rank order: gastrointestinal 47, urogenital 42, lung 36, liver 18, pancreas 18, head and neck 16, hematologic tumor 16, breast 14, and others 12. Survival from diagnosis was 810 ± 1128 days. The mean time from diagnosis to beginning of home palliative care was 739 ± 1099 days, and the mean interval from starting home palliative care to death was 70 ± 110 days. A total of 43 patients (19.3%) did not die at home but were admitted to hospital in the last days of life. No demographic differences were found with other patients.

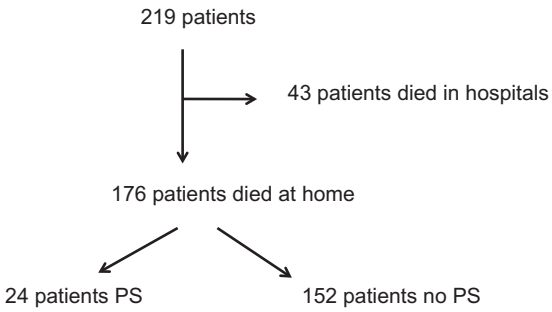

Fig. 1. Flow chart of patients admitted to home care. PS = palliative sedation.

The flow chart of patients is reported in Fig. 1. The PS was performed in 24 of 176 patients who died at home (13.6%). The characteristics of these patients are reported in Table 1. The mean age of these 24 patients was 67 ± 19 years, and 10 (41.7%) were male. The PS occurred more frequently in younger patients ($P = 0.012$; analysis of variance test), whereas no differences in gender were found ($P = 0.325$; Chi-squared test).

The principal reasons to begin PS were agitated delirium ($n = 20$) and dyspnea ($n = 4$). At the time, the decision was made to begin PS, the patients were not able to be involved in the decision because of their clinical conditions. After starting PS, it was continued until death; none of the patients' relatives asked for sedation to be discontinued. The mean duration of PS was 42.2 ± 30.4 hours. Table 2 provides data on the mean daily doses of opioids, sedatives, and symptomatic agents used during PS in the 24 patients. In Table 3, mean values of symptom intensity, Communication Capacity Scale scores, and Agitation Distress Scale scores are described. In most cases after starting PS, pain was no longer evaluated because of deep sedation or altered consciousness. Other symptoms were based on the judgment of proxies.

The level of satisfaction for the home care team was optimal, good, and fair in 18, five, and one case(s), respectively. The level of satisfaction for relatives was optimal, good, and fair in 15, eight, and one case(s), respectively. No differences between home care team and relatives were found ($P = 0.261$; Chi-squared test).

Discussion

This is the first prospective study of PS performed at home. The principal reason to begin PS was agitated delirium, with dyspnea being the second indication in about 20% of

Table 1
Characteristics of Patients Who Received PS

Age (y)	Gender	Diagnosis	PS Indication	Proposing	Duration (h)	Team Satisfaction	Family Satisfaction
87	Female	Brain	Delirium	Team-family	72	Optimal	Optimal
78	Male	Lung	Delirium	Team-family	17	Optimal	Optimal
80	Male	LMA	Delirium	Team	8	Fair	Optimal
85	Female	Parotid	Delirium	Team-family	96	Optimal	Optimal
70	Male	Liver	Delirium	Team-family	28	Optimal	Optimal
72	Female	Pancreas	Delirium	Team	27	Optimal	Good
54	Female	Breast	Delirium	Team	25	Optimal	Optimal
24	Male	LNH	Delirium	Team	36	Optimal	Optimal
86	Male	Head-neck	Dyspnea	Team	6	Optimal	Optimal
60	Female	Liver	Delirium	Team	45	Optimal	Optimal
45	Male	Colon	Delirium	Team	31	Optimal	Optimal
66	Male	Liver	Delirium	Team	53	Optimal	Good
73	Female	Stomach	Delirium	Team	34	Good	Optimal
81	Male	Prostate	Delirium	Team	94	Optimal	Optimal
79	Male	Rectum	Dyspnea	Team	1	Optimal	Good
89	Female	Colon	Delirium	Team	82	Good	Optimal
51	Female	Colon	Delirium	Team	16	Optimal	Good
34	Female	Liver	Dyspnea	Team-family	26	Optimal	Optimal
98	Female	Ovarian	Delirium	Team	37	Optimal	Good
67	Male	Colon	Delirium	Team-family	100	Optimal	Optimal
44	Female	Sarcoma	Dyspnea	Team	88	Good	Good
62	Female	Colon	Delirium	Team	34	Good	Fair
79	Female	Head-neck	Delirium	Team	14	Good	Good
54	Female	Pancreas	Delirium	Team-family	44	Optimal	Good

PS = palliative sedation; LMA = leukemia; LNH = non-Hodgkin lymphoma.

Table 2
Drugs Used During Palliative Sedation

	T0 ($N=24$)	T1 ($N=20$)	T2 ($N=8$)	T3 ($N=6$)	T4 ($N=3$)
Drugs	*n*; mean (SD) daily dose, mg				
Subcutaneous morphine	9; 86 (28)	8; 77 (38)	5; 78 (41)	4; 71 (44)	2; 75 (21)
Intravenous morphine	12; 168 (328)	11; 199 (354)	3; 490 (615)	2; 720 (678)	1; 240
Transdermal fentanyl, μg/h (SD)	3; 80 (45.8)				
Midazolam	24; 27 (3.9)	20; 38 (17)	8; 56 (31)	6; 58 (36)	3; 53 (25)
Butylscopolamine	7; 88 (30)	8; 82 (25)	5; 84 (26)	4; 75 (30)	2; 60 (0.0)
Haloperidol	11; 9.4 (3.6)	9; 9.7 (2.5)	2; 12.5 (3.5)	2; 12.5 (3.5)	1; 10
Chlorpromazine	1; 200	1; 400	4; 225 (163)	3; 300 (141)	1; 400
Furosemide	0	2; 30 (14)	2; 30 (14)	1; 20	0

SD = standard deviation.

patients. This is in accordance with previous retrospective studies performed at home by our group and other authors,[7,10,11] and in contrast with older data.[12,13] It is likely that a modern approach and greater opioid availability make pain an infrequent indication for PS. Younger patients were more frequently sedated before death. Possibly, younger patients may be more aggressively treated and may present more complex clinical situations in the last days of life.[8] Of interest, the decision to begin PS was proposed by the home palliative care team on the basis of clinical need. However, relatives shared this decision, and no conflicts emerged, as demonstrated by the absence of discontinuation of PS by request of relatives. From a clinical standpoint, discontinuation was unlikely to maintain an acceptable level of symptom control. Generally, information about patients' or relatives' requests is poor and unclear, given the retrospective nature of most studies performed at home; and that, in the Italian culture, advance directives are seldom provided, although in a Spanish study the decision to start PS was made with the patient in 45% of the cases.[14] In previous studies performed at home, no clear documentation has been reported regarding the involvement in the decision-making process immediately before starting PS. Circumstances in which the decision has been made may be different: whether PS was planned ahead or was needed urgently, whether the preferences of the dying patient were known, or whether the emotional difficulties encountered in controlling the patient's symptoms during the last days of life were components in the decision to sedate the patient. The onset of PS often corresponds to a moment in which the patient is no longer collaborating.[8] Indeed, consent and decision to start PS have a different meaning, and patients are unlikely to provide or share a decision because of cognitive impairment (delirium) or severe suffering (dyspnea). It is reasonable that the clinical need to start PS be proposed by an expert team, explaining to family members the further steps and the possible options of intervention, unless there is an advance directive provided by the patient. This finding is unlikely in the Mediterranean

Table 3
Parameters Recorded During PS at the T0–T4 Time Intervals

	T0 ($N=24$)	T1 ($N=20$)	T2 ($N=8$)	T3 ($N=6$)	T4 ($N=3$)
Parameters	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Pain	1.7 (2.4)	NV	NV	NV	NV
Delirium (24 patients)	5.9 (3.4)	1.4 (2.2)	0.6 (1.7)	0	0
Delirium (20 patients[a])	6.9 (2.7)	1.6 (2.3)	0.7 (1.9)	0	0
Dyspnea (24 patients)	2.9 (4.0)	0.7 (1.9)	0	0	0
Dyspnea (4 patients[a])	9.3 (0.9)	0.0 (0.0)	0	0	0
Communication Capacity Scale	12.3 (3.2)	16.4 (0.7)	16.6 (0.7)	16.7 (0.8)	17
Agitation Distress Scale	9.7 (4.8)	2.4 (3.3)	1.1 (1.6)	0.5 (0.6)	1
Death rattle	0.3 (0.8)	0.5 (0.9)	0.9 (1.3)	0.5 (1.2)	1 (1)

PS = palliative sedation; SD = standard deviation; NV = non-evaluable.
[a]Mean data for patients who were sedated only for delirium (20 patients) and for dyspnea (4 patients).

culture, which is disposed to less autonomy and/or a higher level of confidence in health professionals.[15]

The PS was highly effective, as confirmed by the progressive decrease of symptom intensity, although at this stage most symptoms were indirectly evaluated by relatives, and could not be expressed through verbal report by the patient. Satisfaction with PS was quite high, and considered good or optimal in almost all cases by both professionals and relatives.

According to the protocol, a stepwise approach was used, starting with midazolam. Doses of midazolam were slightly increased 24 hours after starting PS, according to the clinical needs and the level of unconsciousness necessary to control symptoms. Then, a small number of patients who survived more than 24 hours required further dose increments, with an escalation index of about one in the three patients who survived four days, with doses even lower than those reported in other studies.[11] Of interest, the use of midazolam out of hospital, subcutaneously or intravenously, is off-label, although both home care programs have direct contact with hospitals or hospices and drugs are provided by these institutions.

To monitor the effectiveness of PS, validated tools were used.[9] The Agitation Distress Scale score progressively decreased immediately after starting PS. Similarly, the Communication Capacity Scale, which demonstrated impaired communication before starting PS, reached almost the maximum score (no communication at all) subsequently.

A high proportion of patients died at home. These data are quite impressive in comparison with data reported in the literature. Specialized home care has been shown to be associated with reduced inpatient deaths and overall hospitalization over the last two months of life in comparison with patients living in areas devoid of home palliative care services.[14] In comparison with areas with no palliative care services, hospital death frequency was lower (61%) in the palliative home care areas. The findings of this study show that most patients could die at home; about 13% of them required PS according to an a priori definition and using a specific protocol. It would be interesting to know the pathways of the 43 patients (about 20%) admitted to home care programs, who did not die at home and were admitted to hospital. Unfortunately, this information was unavailable. This aspect should be evaluated in future studies.

Mean survival from the start of PS was relatively short, less than two days, confirming previous observations and that patients were really at the end of life.[8] Of interest, it also was observed that survival from the start of palliative care was even longer in patients who were sedated. This finding potentially confirms the beneficial role of PS performed at home, without interfering or anticipating death, as reported in other settings.[16,17] However, as in many other studies, the group that did not require PS had varying end-of-life trajectories and survival estimates must consider many other factors.

Death rattle frequently occurs in the dying patient, occurring in 23–92%. Death rattle results from an accumulation of secretions in the pharynx and/or airways in the absence of effective reflexes for swallowing and coughing.[18] This may more frequently occur in patients with a low level of consciousness such as sedated patients. In this study, where death rattle was prospectively assessed and treated according to a determined protocol, death rattle intensity was relatively low, confirming that careful monitoring and adequate treatment may be successful, even at home.

A limitation of this study, which may affect the results, concerns the design, which is that of a prospective cohort study. As a consequence, the statistical results may not always be reliable, especially without a large sample size because of the inability to ensure that study groups are truly comparable at baseline. In fact, without true randomization at baseline, it is unlikely that differences in the comparison groups can be controlled for effectively. However, we must consider the difficulty in carrying out this kind of study under ideal conditions given the critically ill patients involved. The results of this study, however, may be useful in terms of the clinical management of PS.

In conclusion, PS performed at home is a feasible and effective method to relieve intractable symptoms in the last days of life. It would be interesting to evaluate the possible differences existing among different home care systems, hospices, or acute palliative care

units. Finally, more information should be gathered on the specific services provided by the local network of palliative care.

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