

Opioid Use at the End of Life and Survival in a Hospital at Home Unit

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Abstract

Background and significance: Although opioids are commonly used to treat pain, dyspnea, and other symptoms at the end of life, little information is available on the safety and efficacy of the use of these medications in terminally ill patients in the home care setting.

Objectives: To explore whether high doses of opioids, or increasing doses, influence survival in patients with terminal cancer in a Hospital at Home unit.

Methodology: A retrospective cohort study. Clinical records of 223 oncologic patients admitted to the Hospital at Home unit of Hospital Galdakao-Usansolo from 2003 to 2007 and who died at home were reviewed. Demographic variables (age and gender) as well as clinical variables at the time of admission (Eastern Cooperative Oncology Group Performance Status scale, previous intake of opioids, type of cancer, use of coadjuvant drugs) and daily doses of morphine during the admission were recorded. Main outcomes were the number of days from the maximum dose of opioids administered to death and total length of survival during the admission.

Results: Median survival from day of maximum dose to death was longer for patients who received higher doses of opioids (6 days) than those who received lower doses (2 days; $p = 0.010$). These differences disappeared after adjusting by demographic and clinical variables (HR, 0.86; 95% CI, 0.62–1.18 [$p = 0.338$]). Patients who received more than twofold increases in their initial doses had longer median survival (22 days) than those who did not (9 days; hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.34–0.60 [$p < 0.0001$]); these differences persisted after adjustment.

Conclusions: Our results suggest that the use of opioids is safe in for use in Hospital at Home patients with cancer and is not associated with reduced survival.

Introduction

RELIEVING PAIN AND SUFFERING is an essential part of palliative care. Although opioids have traditionally been used to control pain and dyspnea in end-of-life care, use of these medications remains controversial. While some experts have raised concerns that the use of opioids may further shorten survival,^{1,2} several studies have shown that opioids do not affect survival^{3–5} and in the clinical experience of palliative care physicians they are important medications for the comfort of dying patients. Much has been said about this conflict in medical journals and by policy makers.^{6–9}

Some clinicians and ethicists use the doctrine of double effect to defend or justify the use of opioids in palliative care. In brief, it states that an action that causes a serious adverse effect that has been foreseen—including death—may be morally justified if the intention behind the action was to do

good and the adverse effect was not the means of achieving the good outcome.¹⁰ It is possible that the double effect defense is not needed to justify the use of opioids in end-of-life palliative care. Several studies have demonstrated no direct association between administration of opioids and death in end-of-life care.^{3,5,11} However, most of these studies have been conducted in the hospital or hospice setting, where physicians have better control over the use of opioids and can quickly respond to adverse effects.

Hospital at Home units offer specialized medical and nursing care to patients who can be provided with assistance and active monitoring that is too complex for primary care but appropriate for a patient's home.¹² This approach has benefits on many levels. For patients, it is associated with fewer hospital-associated problems, better assessment of the aids and adaptations in the home setting, and improvement in well-being, because patients are evolved in the decision-making

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Accepted April 15, 2010.

process.^{12,13} It benefits the health service by reducing or avoiding costly hospital stays, reducing elective surgical waiting lists, and reducing the cost of care. Health workers benefit from the active collaboration of family members. Hospital at Home also serves as a link between the hospital and ambulatory settings. In Spain, Hospital at Home units have been leaders in the development of palliative care.¹⁴

Few studies have examined the safety and efficacy of opioids and other palliative medications, such as sedatives, that are commonly prescribed in the Hospital at Home setting. We conducted this study to determine if the use of opioids to control pain, dyspnea, or other symptoms among patients with terminal stage cancer treated at home influence survival.

Methods

This retrospective cohort study used data derived from clinical records of the Hospital at Home unit of the Hospital Galdakao-Usansolo. This 439-bed teaching hospital in the Basque Country (northern Spain) serves a population of 300,000 inhabitants. It belongs to the network of public hospitals of the Basque Health Care Service, which provides free unrestricted care to nearly 100% of the population. The Hospital at Home unit, established in 1993, provides home-based care to patients who are eligible for the program and who agree to it as an alternative to hospitalization. Care is provided by six physicians experienced in palliative care and a dedicated team of nurses. Because of the geographic dispersion of the Hospital at Home patients, the whole primary care population of the area is not covered. During the study period our Unit was serving 14 towns with a total population of 159,822 inhabitants. According EUSTAT (Basque national statistics organization) 1394 patients died of cancer in our coverage area in that period and of those 669 died in their homes. Data for 223 (33%) of these subjects are presented here whereas the rest of the patients were attended by primary care groups.

Patients eligible for the study included those older than 18 years who were admitted to the unit from 2003 to 2007 with terminal stage cancer, defined as "terminal phase in which advanced disease is in a progressive and irreversible stage with multiple symptoms, emotional impact, loss of autonomy, with very little or no capacity to respond to specific treatment and with a limited life expectancy (weeks or months), in a context of progressive fragility"¹⁵ and who died at home. Hospital at Home patients with cancer who died in a hospital setting were excluded from the study.

Medical records were reviewed by a single physician (I.B.), who was also a member of the Hospital at Home unit. The hospital's Ethics Committee approved the study.

Measures

Sociodemographic variables (age and gender), Eastern Cooperative Oncology Group Performance status (ECOG-PS) scale¹⁶ at the time the patient was admitted to the unit, previous intake of opioids, type and stage of cancer, number of metastases, concomitant use of other medications (midazolam, others), and demanding service were collected. Daily doses of morphine were also recorded. As patients were taking different kinds of opioids, for all analyses presented here opioid doses were converted into milligrams equivalent to oral morphine OME.^{4,5,17}

We created a variable named "doses" with two categories: regular (maximum doses of oral morphine less than 120 mg) and high (maximum doses equal or greater than 120 mg). We also created another variable named "dose escalation" with two categories: modest dose escalation included patients who never received doses of morphine that were 2 times as large as the dose when entering the unit, and doubled dose included patients who received one or more doses of morphine during the last week of life that were at least twice as large as their starting dose. Among patients who were not taking opioids at the time of admission, those who were administered any dose of morphine of at least 30 mg in the last week of life were included in the doubled dose category. For patients who survived for 7 days or fewer, all survival days were considered.

Outcomes

The primary outcomes of interest were (1) the time in days from maximum administered dose of opioids to death and (2) total survival in days associated with dose escalation in the last week of life.

Statistical analysis

Categorical variables are presented as frequencies with percentages; continuous variables as means and standard deviations (SD). The χ^2 for trend and Fisher's exact test were implemented to test for associations between categorical variables. The *t* test was used for comparisons of continuous variables. The outcomes of survival time from maximum dose received and total survival are described with medians and comparisons between the groups of interest, made with the log rank test. 95% confidence intervals (CI) for median survival were calculated.¹⁸

The survival of different groups was further examined with Cox regression analysis after adjusting for age, gender, performance status (ECOG-PS 1 to 5, previous use of opioids (yes, no), and use of coadjuvant medications (morphine only, morphine and other) Breslow's approximation was used for tied data. No censored observations existed in this data set.

The proportional hazard (PH) assumption of all variables entered in the Cox regression model was assessed graphically and with Schoenfeld's residual test.²² When the PH assumption was not fulfilled, adjustment was done by stratification. Results of the Cox regression analysis are presented as hazard ratios (HR) with 95% CIs.

All statistical analyses were done with SAS version 9.0. Graphs were designed with SPSS version 16.0 (SPSS Inc., Chicago, IL).

Results

From January 2003 to December 2007, 1,475 patients were admitted to our Hospital at Home unit, 231 of whom had terminal cancer. Of these, 8 patients died in a hospital, leaving a final sample of 223 patients who died at home. The mean (SD) age was 68 (12) years, 61% were male, and 54% were completely dependent (ECOG-PS4) No patients in PS5 were encountered in this dataset (Table 1). The most common primary tumors were those involving the digestive tract; 89% of the patients had no or one metastasis. Prior to admission in the Hospital at Home unit, 44% of the patients had been taking

TABLE 1. BASELINE CHARACTERISTICS OF THE SAMPLE ACCORDING TO THE OPIOID DOSES ADMINISTERED

Variable	Maximum dose received		p value
	Regular doses (< 120 mg) n = 124	High doses (≥ 120 mg) n = 99	
Mean age (SD)	71.4 (11.9)	65.8 (10.8)	0.0004
Female, n (%)	51 (41.1)	35 (35.4)	0.379
Previous intake of opioids, n (%)	28 (22.6)	71 (71.7)	<0.0001
Number of metastases			0.116
0	58 (46.8)	35 (35.4)	
1	53 (42.7)	52 (52.5)	
2	11 (8.9)	8 (8.1)	
3	2 (1.6)	4 (4.0)	
Coadjuvant medications	60 (48.4)	50 (50.5)	0.753
Type of cancer, n (%)			0.125
Respiratory	20 (16.1)	26 (26.3)	
Digestive	57 (46.0)	44 (44.4)	
Gynecologic	13 (10.5)	7 (7.1)	
Urologic	11 (8.9)	11 (11.1)	
Nervous system	9 (7.3)	1 (1.0)	
Other	14 (11.3)	10 (10.1)	
Performance Status, n (%)			0.823
PS-2	11 (8.9)	10 (10.1)	
PS-3	44 (35.5)	38 (38.4)	
PS-4	69 (55.6)	51 (51.5)	

SD, standard deviation.

opioids, and 51% took other medications in addition to opioids. During the last week of life, 44% of the patients received an increase in their opioid dose that was at least twofold higher than their initial opioid dose.

Comparing patients who received regular doses of morphine (maximum dose less than 120 mg) and those who received high doses (maximum dose 120 mg or more), the only statistically significant differences were in age ($p = 0.0004$) and prior opioid intake ($p < 0.0001$); no statistically significant differences were observed in gender, location of primary tumor, number of metastases, ECOG-PS status, or use of concomitant medications (Table 1). When comparing patients by dose escalation, the only statistically significant differences between those with modest escalation and those with doubled doses were observed in performance status ($p = 0.004$) and prior opioid intake ($p = 0.0002$). The modest-escalation group ($n = 156$), had a higher percentage of completely dependent patients, i.e., PS4 = 95 (61%) compared to the double-escalation group ($n = 67$), with PS4 = 25 (37%).

Median survival from day of maximum dose to death was 2 days (95% CI, 1–4) for those who received regular doses and 6 days (95% CI, 3–9) for those who received higher doses. The p value for the log rank test was 0.010. Figure 1 shows differences in survival in the two groups. Those who received higher doses had a lower hazard compared to those who received regular doses (HR, 0.72; 95% CI, 0.55–0.94 [$p = 0.015$]). The differences disappeared after adjusting for age, gender, performance status, and previous intake of opioids, stratifying by the variable "concomitant use of other medications"

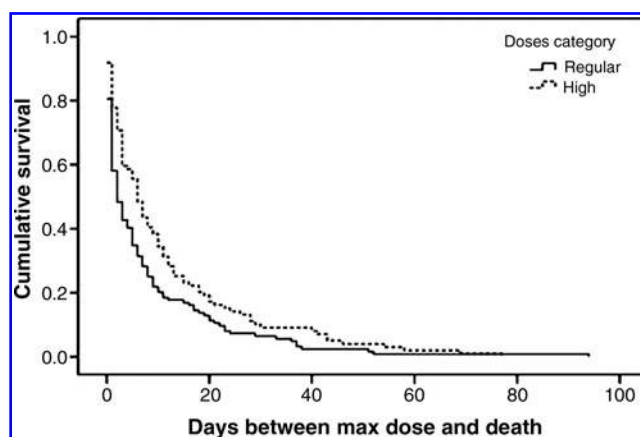


FIG. 1. Kaplan-Meier plot of survival between maximum dose to death for patients in the regular and high-dose opioid groups.

(HR, 0.86; 95% CI, 0.62–1.18 [$p = 0.338$]; Table 2). The R^2 of the total model was 11%.

Total median survival time for those who received doubled doses was 22 days (95% CI, 14–34), compared to 9 days (95% CI, 8–12) for those who did not receive doubled doses. The p value for the log rank test was <0.0001 . As shown in Table 3 and Figure 2, patients who received doubled doses were significantly more likely to have survived longer than those with modest dose escalation (HR, 0.45; 95% CI, 0.34–0.60). These differences persisted even after adjustment by age, gender, performance status, and previous intake of opioids, stratifying by the variable "concomitant use of other medications."

Age and ECOG-PS classification significantly influenced this model. Patient age was associated with probability of death (HR, 1.02; 95% CI, 1.00–1.03 [$p < 0.006$]). Patients classified as PS-4 had a more than two-fold higher hazard ratio for death as those classified as PS-2 (HR, 2.48; 95% CI, 1.44–4.26 [$p = 0.001$]). The R^2 of this model was 23%.

Discussion

In this study of terminally ill patients with cancer treated in a Hospital at Home unit, the use of opioids did not shorten survival. To the contrary, median survival was actually higher for patients who received high doses or doubled doses than for patients who received regular doses or only modest escalations in dose. The results of this study suggest that opioids do not shorten survival at the end of life and support findings of other investigators that opioids are safe to use at the end of life,^{3–5} extending this work to the Hospital at Home setting.

Our study differs from prior investigations in this area in two main ways. First, other studies that have explored the association between opioid dose and survival time have been conducted in the hospital or hospice setting. In these settings, higher doses of opioids than those used in our study are commonly prescribed, in part because physicians feel more comfortable prescribing in a hospital where their patients are completely and continually monitored. Our study was conducted in a Hospital at Home setting, with more limited monitoring. Second, other studies have focused on opioid use in the last hours before death, when the doctrine of double

TABLE 2. MULTIVARIATE COX REGRESSION ANALYSIS RESULTS FOR THE OUTCOME OF TIME IN DAYS FROM MAXIMUM DOSES TO DEATH

Variable	Hazard ratio (95% CI) ^a	p value
Dose ≥ 120 mg	0.86 (0.62–1.18)	0.338
Age	1.02 (1.01–1.04)	0.001
Gender (female)	1.16 (0.88–1.52)	0.303
ECOG-PS		
PS2	1	—
PS3	1.17 (0.70–1.94)	0.551
PS4	1.49 (0.91–2.45)	0.115
Previous intake of opioids	0.82 (0.59–1.12)	0.208

ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; CI, confidence interval. Model R-square: $R^2 = 0.111$.

^aValues adjusted by the variable “coadjuvant medications” by stratification.

effect is assumed to be in play.^{4,6} Our study evaluated opioid use during the entire Hospital at Home stay, from admission until death.

Prior studies exploring the impact of opioid administration at the end of life found, as we did, that opioid administration did not shorten survival.^{3,4} A limited number of studies exploring increases in opioid dosage and survival found no differences in survival times when the change was made few hours before death.^{3,11} We examined change in dosage over a longer period, and observed longer survival times in patients who received doses of opioids twofold or more higher than their initial doses at some point during the last 7 days of life. Whether this reflects a protective effect of opioids in these patients, or can be explained other ways, remains to be determined.

As may have been expected, ECOG performance status was associated with survival time. Patients in the PS-4 category had a twofold increased HR for death compared to patients in the PS-2 category. This could be due to better pain control, which may translate into better quality of life and survival.¹¹

TABLE 3. MULTIVARIATE COX REGRESSION ANALYSIS FOR THE OUTCOME OF TOTAL SURVIVAL (IN DAYS) AT ADMISSION

Variables	Hazard ratio (95% CI) ^b	p value
Doubled doses ^a	0.48 (0.34–0.67)	<0.0001
Age	1.02 (1.00–1.03)	0.017
Gender (female)	1.03 (0.78–1.36)	0.819
ECOG-PS		
PS2	1	—
PS3	1.41 (0.83–2.40)	0.206
PS4	2.48 (1.44–4.26)	0.001
Previous intake of opioids	1.01 (0.75–1.36)	0.947

CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status. Model R-square: $R = 0.227$.

^aPatients who received one or more doses of morphine during the last week of life that were at least twice as large as their starting dose. Opioid-naïve patients were also counted if they had received at least 30 mg of OME.

^bValues adjusted by the variable “coadjuvant medications” by stratification.

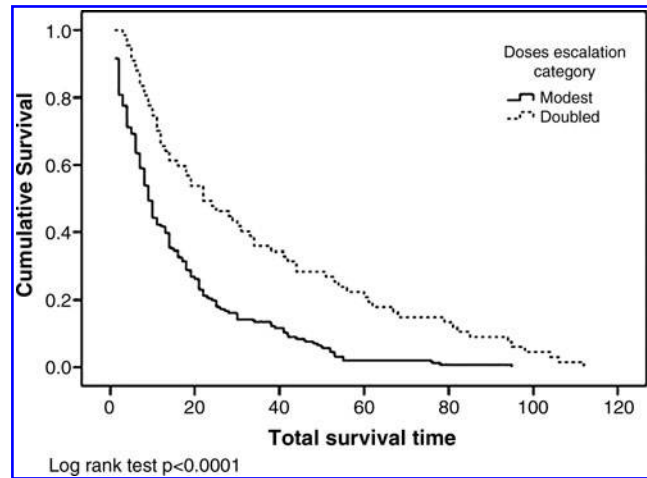


FIG. 2. Kaplan-Meier plot of total survival time for patients in the two-dose escalation groups. Log rank test $p < 0.0001$.

Some patients are referred to the Hospital at Home unit due to poor pain control and not necessarily due to a shorter life expectancy. If so, it is possible that some patients receiving higher doses of morphine survived longer because they may have been in somewhat better general health and/or in an earlier stage of their disease.¹¹ Yet we found no differences among groups of patients in each level of performance status and in prior opioid intake upon admission to the unit. It is possible that the medical services that refer patients to the Hospital at Home unit are more comfortable if the patients are managed by the unit, which visits patients daily, rather than by their primary care provider. It is possible that patients may put more trust in a team coming daily from hospital than in their primary care provider, and this could be acting as a confounder in the association between patient well-being and opioid prescription.

Some experts have suggested that pain neurotransmitters compete with morphine in the respiratory center, which makes it relatively safe to prescribe higher doses of morphine in patients with higher levels of pain.^{19–21} This could explain the lack of a difference in survival among those patients who are treated with higher doses of morphine and those with lower doses, since it is supposed that those treated with higher doses refer more pain.

We used univariate and multivariate Cox regression models to explore the effect of high doses of opioids and doubled doses on the survival of terminally ill patients admitted to a Hospital at Home unit. As far as we know, this is the first time that Cox regression specifically designed for handling survival data²² has been implemented in this setting; previous authors have used linear and logistic regression analyses. Nevertheless, the conclusions we have reached are quite similar to those of previous studies in the subject.^{3–5} Another strength of our study is related to the setting in which the study was performed, the home-care setting, where the safety of opioid prescription has not been previously evaluated. Several limitations, generally related to retrospective design, must also be noted. Since the sample was not randomly determined, other variables or residual confounders could explain differences between groups, which could explain the low R^2 values. Another limitation is that the patients

were admitted into the Hospital at Home unit at different stages of the natural history of their disease. We tried to control for this by including ECOG-PS in the model, which is predictive of disease progression.

In conclusion, we explored the efficacy and safety of opioid use during the entire stay of patients with terminal stage cancer in a Hospital at Home unit, not only during the very end of their lives. We found that the use of opioids, even high-dose opioids or escalating doses, did not shorten survival.

Author Disclosure Statement

No competing financial interests exist.

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