Original Article

Morphine for Dyspnea Control in Terminal Cancer Patients: Is It Appropriate in Taiwan?

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Abstract

Morphine for dyspnea control usually arouses ethical controversy in terminal cancer care. This study prospectively assessed the use of morphine for dyspnea control in terminal cancer patients in terms of two characteristics: the extent to which medical staff, family, and patients found morphine to be ethically acceptable and efficacious, and the influence of morphine on survival. One hundred and thirty-six palliative care patients meeting specific eligibility criteria were enrolled. A structured data collection form was used daily to evaluate clinical conditions, which were analyzed at the time of admission and 48 h before death. Sixty-six (48.6%) of the 136 patients had dyspnea on admission. The intensity was mild in 14.0% and moderate or severe in 34.6%. The intensity of dyspnea became worse 48 h before death (4.29 ± 2.55 vs. 4.94 ± 2.60, $P < 0.001$*, range 0–10). Twenty-seven (40.9%) of 66 patients with dyspnea received morphine on admission for the control of dyspnea; the routes of administration were oral (59.3%) and subcutaneous (40.7%). Fewer than two-thirds (59.3%) of the patients were given morphine with the consent of both patient and family. More than one-third (40.7%) on admission and about one-half (52.8%) in the 48 h before death had the consent of family alone. Positive ethical acceptability and satisfaction with using morphine for dyspnea control were found in both medical staff and family in this study. Multiple Cox regression analysis showed that using morphine for dyspnea, both on admission and in the 48 h before death, did not significantly influence the patients' survival (HR: 0.015, 95% CI: 0.00–4.23; HR: 1.76, 95% CI: 0.73–4.24). In this population, the use of morphine for dyspnea control in the terminal phase of cancer was effective and ethically validated in the study. Research efforts to find the most appropriate route and dosage of morphine for dyspnea, based on the patient's situation, remain worthwhile.* J Pain Symptom Manage 2004;28:356–363.

Key Words

Morphine, terminal cancer, dyspnea

Introduction

Dyspnea is one of the most distressing symptoms of terminal cancer patients. Studies have shown that up to 50%–70% of terminal cancer

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patients experience dyspnea in the last six weeks of life and the symptom is aggravated with the progression of disease. Dyspnea is often accompanied by anxiety and fear, which severely hampers the quality of life of terminal cancer patients.[1–7] A study in Taiwan showed that 56.6% of terminal cancer patients develop dyspnea and half rated the symptom as moderate or severe.[8] The symptom was usually persisting, uncontrollable and aggravated. The problem of dyspnea greatly challenges the goal of a good death and also deeply bothers family and medical professionals. Therefore, management of dyspnea has become one of the most important issues in palliative care.

Although pharmacological and non-pharmacological interventions have been used to treat dyspnea in palliative care, outcome data are limited.[9,10] Morphine has been found to be effective in the management of cancer dyspnea,[11–14] but some ethical concerns and cultural adaptations usually arise due to its depressant action on the respiratory center and misconceptions regarding opioids.[15–17] These problems are encountered commonly in Asian countries, and have not been addressed in previous studies. It has been advocated that during the terminal stages of a patient's illness, when assessment tools are no longer feasible or possible, that a "breathing comfortably" approach be adopted for patient and family comfort.[18] Thus, it is also worthwhile to investigate whether patients, families, and medical staff have been satisfied with treatment. The aims of this study were to investigate the use of morphine for dyspnea control in terminal cancer patients in terms of two characteristics: the extent to which medical staff, family, and patients found morphine to be ethically acceptable and efficacious, and the influence of morphine use on survivals.

Methods

Patients

All consecutive patients admitted to the hospice and palliative care unit of National Taiwan University Hospital between May 2001 and the end of January 2002 were recruited for the study. Patients whose cancers were not responsive to curative treatment were identified in an initial assessment performed by members of the Admissions Committee. Patients who met the following inclusion criteria were considered eligible for our study: 1) the patient was conscious and communicative at the time of admission; 2) considering the cultural practice, the study accepted oral informed consent, either by patients or their family; 3) the patient was not so weak that answering the questions would be a major burden; and 4) survival time exceeded at least two days after admission. The patients' primary care physicians and nurses involved in the care of the patients determined their eligibility. The selection of patients and design of this study were approved by the Ethics Committee in the hospital. By the end of the study period, 136 of the 271 consecutive patients met the inclusion criteria and had completed the study.

Instrument

An assessment form, which was used daily, was designed after a careful review of the literature in this area. It included demographic data, dyspnea score (on a 0–10 scale), use of morphine with the intention of dyspnea control (including the consent for using morphine), date of administration, route of administration (oral, subcutaneous, intravenous, transdermal), frequency and dosage (equivalent dose of intravenous morphine), positive effects, and untoward effects of using morphine. Ethical acceptability and satisfaction with morphine for dyspnea control of medical staff, family and patients were also recorded. The entire form was tested for content validity by a panel comprising two physicians, two nurses, and one psychologist, all of whom were experienced in the care of the terminally ill. Each item in the questionnaire was appraised from "very inappropriate and not relevant (1)" to "very appropriate and relevant (5)." A content validity index (CVI) was used to determine the validity of the structured questionnaire and yielded a CVI of 0.952. In addition, a pilot study was conducted for one month in the same unit. This pilot study further confirmed the instrument's content validity and ease of application.

Demographic characteristics assessed included gender, age, education, primary tumor sites, metastasis sites, and survival. The instrument for measuring dyspnea used in the study was a modified Borg scale, introduced in 1982 as a category scale with ratio properties, and

adapted by Burdon et al. to measure the intensity of the sensation of dyspnea.[19] The self-report scale consists of a vertical scale labeled 0 to 10, with corresponding verbal expressions of progressively increasing sensation intensity such as "nothing at all" to "maximal," and is the format most commonly used.[19–22] Currently, the modified Borg scale is frequently used in Taiwan because it is easier for patients to understand and the local medical staff is familiar with it.

The untoward effects of morphine use for dyspnea control included the following: "consciousness change" was defined as "somnolence, dizziness, mental clouding, or hallucinations at the time of treatment with morphine;" "decrease respiratory rate" meant "decrease in respiratory rate to less than 10 times per minute," since it is easier clinically to assess the morphine-induced respiratory depression by observing the change of respiratory rate; "suppressed CV function" indicated "the reduction of the systolic blood pressure by more than 20 mmHg at the time of morphine treatment;" "death due to morphine" was defined as "death is considered related to the morphine use." Ethical acceptability was assessed ("should provide morphine," "might be right," or "should not provide morphine") to investigate whether or not using morphine to control dyspnea, for medical staff and families, was ethically acceptable. Regarding the efficacy of the use of morphine, the medical staff rated themselves and asked patients and families about the levels of satisfaction (yes, fair, or no) toward the improvement of dyspnea.

Procedure

The prevalence of dyspnea and the use of morphine for dyspnea control were recorded daily by staff members. They assessed and recorded the presence or absence of dyspnea, its severity (average level of dyspnea over the last 24 hours), and the details of using morphine. These data were assessed and subsequently analyzed at the time of admission and 48 hours prior to death (retrospectively) in weekly team meetings. Moreover, we analyzed the clinical circumstances of each case and investigated the satisfaction and ethical acceptability among patients, families, and staff in decision making relating to the use of morphine for dyspnea control on the basis of moral discussions in the 50 weekly team meetings held during the study period. The decision to use morphine to control dyspnea after admission was always made on the basis of consultation among medical staff, patients and families.

Statistical Analysis

Data management and statistical analysis were performed using SPSS 11.0 statistical software (SPSS, Chicago, IL). A frequency distribution was used to describe the demographic data and the distribution of each variable. Mean values and standard deviations were used to analyze the severity of dyspnea. A paired *t*-test was used to compare the differences in the severity of dyspnea at different times. Univariate analysis was performed for the difference in survival by independent sample *t*-test and Pearson correlation coefficients. Multiple Cox regression analysis was used to examine the influence of the following factors on survival: gender, age, primary cancer site, metastasis site, consciousness level (clear or drowsiness), dyspnea score (≤ 5 or >5), and the use of morphine including the route and dosage. A *P*-value less than 0.05 was considered statistically significant.

Results

Of 271 consecutive patients with terminal cancer, 136 were conscious on admission and met eligibility criteria. Reasons for ineligibility were: confusion and altered mental status ($n = 44$), too weak to participate ($n = 25$), died within two days of admission ($n = 25$), patient or family refusal ($n = 23$), and communication impairment ($n = 8$). Of 136 eligible patients, 77 (56.6%) were men, and 59 (43.4%) were women (Table 1). One-half of the 136 patients (50.7%) were older than 65 years, and only three patients were younger than 18 years. The primary sites of cancer were lung (16.4%), liver (14.0%), colorectal (11.8%), and pancreas (8.8%); 31 of 136 patients (22.8%) had lung metastasis. For patients who died, the mean survival time after admission was 23.62 ± 22.93 days.

Table 2 shows the prevalence and severity of dyspnea. In order to obtain more reliable data, we selected patients who were communicative on admission and prospectively assessed their

Table 1
Demographic Characteristics of Patients (n = 136)

Variable	n (%)
Sex	
Male	77 (56.6)
Female	59 (43.4)
Age group (years)	
≤18	3 (2.2)
19–35	6 (4.4)
36–50	27 (19.9)
51–64	31 (22.8)
≥65	69 (50.7)
Primary sites of tumor	
Lung	23 (16.9)
Liver	19 (14.0)
Colorectal	16 (11.8)
Pancreas	12 (8.8)
Stomach	11 (8.1)
Uncertain	3 (2.2)
Cervical/Uterine	8 (5.9)
Head and neck	4 (2.9)
Other	45 (33.1)
Metastasis	
Bone	47 (34.6)
Liver	33 (24.3)
Lung	31 (22.8)
Brain	20 (14.7)
Other	55 (40.4)
Survival days	
2–3	11 (8.1)
4–6	21 (15.5)
7–13	25 (18.4)
≥14	58 (42.6)
Mean ± S.D. (range)	23.62 ± 22.93 (2–123)
Still alive	21 (15.4)

severity of dyspnea daily until their death. Although many patients in the study also had consciousness change 48 h prior to death, the severity of dyspnea in most of those patients still could be assessed. Only 14 of the 115 who died became deeply comatose 48 h prior to death. Sixty-six patients (48.6%) manifested dyspnea at the time of admission, which was rated mild (<3) in 19 patients (14.0%) and moderate or severe in 47 (34.6%). The causes of dyspnea in the 66 patients with dyspnea at admission included anemia (56.1%), pleural effusion (50.0%), lung mass (45.4%), cachexia (44.0%), and lymphangitis (40.9%). There were also 66 patients (65.4%) who suffered dyspnea two days prior to death, with moderate or severe dyspnea in 52.5%. The mean dyspnea score two days prior to death was significantly higher compared with admission ($t = -5.367$, $P < 0.001$), indicating the refractory nature of dyspnea in the very terminal stage.

Eighty-six of 136 patients (63.2%) had been prescribed morphine for their pain prior to the time of admission. The study investigated the use of morphine intended to control the dyspnea. Sixty-six patients manifested dyspnea at admission, of whom 27 patients (40.9%) used morphine (Table 3). The routes of administration included oral in 15 (55.6%) and subcutaneous in 9 (33.3%). Among the 66 patients with dyspnea prior to death, 36 (54.5%) used morphine to control dyspnea; the subcutaneous (58.3%) route became the mainstay of administration and only 22.2% were still able to receive oral administration. Although patients' autonomy was respected, there was a rather high percentage of consent for the use of morphine from families only (40.7% at admission and 52.8% prior the death), rather than from the patients. As far as the untoward effects, only one patient appeared to have signs of respiratory suppression after using morphine, both at the time of admission and two days prior to death.

The satisfaction and ethical acceptability of using morphine for dyspnea is shown in Table 4. The ethical acceptability by both medical staff and families toward the use of morphine were both above 90%. The families of 5 patients (13.9%) and their medical staff were not satisfied with the effect of controlling dyspnea with

Table 2
Severity of Dyspnea

	Admission		Two days prior to death	
	n	%	n	%
Dyspnea				
None	70	51.5	35	34.7
Mild (<3)	19	14.0	13	12.9
Moderate and servere (≥3)	47	34.6	53	52.4
Total	136	100.0	101	100.0
Mean ± S.D. (range)	4.29 ± 2.55	(0–10)	4.94 ± 2.60[a]	(0–10)

[a]Admission vs. two days prior to death—t value = −5.367; P value < 0.001.

Table 3
Content of Using Morphine for Dyspnea Control

	Admission		Two days prior of death	
	n	%	*n*	%
Use of morphine for dyspnea				
Yes	27	40.9	36	54.5
No	39	59.1	30	46.9
Total	66	100.0	66	100.0
Route				
Oral	15	55.6	8	22.2
Subcutaneous	9	33.3	21	58.3
Intravenous	0	0.0	1	2.8
Oral + transdermal	1	3.7	1	2.8
Subcutaneous + transdermal	2	7.4	4	11.1
Intravenous + transdermal	0	0.0	1	2.8
Equivalent dose of IV morphine per day	37.65 ± 38.61 mg		44.69 ± 52.33 mg	
Mean ± S.D. (range)	(4.8–150)		(4.8–240)	
Consent				
Family and patient	16	59.3	17	47.2
Family only	11	40.7	19	52.8
Patient only	0	0.0	0	0.0
Untoward effects of morphine				
No	25	92.6	35	97.3
Consciousness change	1	3.7	0	0.0
Decreased RR	1	3.7	1	2.7
Suppressed CV function	0	0.0	0	0.0
Death	0	0.0	0	0.0

RR, respiratory rate, CV, cardiovascular.

morphine prior to death. Fourteen of 19 patients (73.7%) who were capable of evaluating the effects of morphine were satisfied with its use, although it was difficult to evaluate in the other 17 patients with consciousness disturbance prior to death. There were a number of patients ($n = 5$ at admission and $n = 5$ prior to the death) who reported only fair effects of morphine for their dyspnea.

Table 5 shows the influence of using morphine on patients' survival. Multiple Cox regression analysis showed that using morphine

Table 4
Satisfaction With and Ethical Acceptability of Morphine Use

	Admission		Two days prior to death	
	n	%	*n*	%
Ethical acceptability of medical staff				
Should provide morphine	27	100.0	36	100.0
Might be right	0	0.0	0	0.0
Medical staff satisfaction				
Yes	26	96.3	31	86.1
Fair	1	3.7	4	11.1
No	0	0.0	1	2.8
Ethical acceptability of family				
Should provide morphine	26	96.3	35	97.2
Might be right	1	3.7	1	2.8
Family satisfaction				
Yes	24	88.9	30	83.3
Fair	3	11.1	5	13.9
No	0	0.0	0	0.0
Unavailable	0	0.0	1	2.8
Patient satisfaction				
Yes	16	59.3	14	38.9
Fair	5	18.5	5	13.9
No	0	0.0	0	0.0
Unavailable	6	22.2	17	47.2
Total	27	100.0	36	100.0

Table 5
Influence of Morphine Use for Dyspnea on the Survival of Patients By Using Multiple Cox Regression

	Hazard ratios (95% CI)	*P*-value
Using morphine at the time of admission	0.015 (0.00–4.23)	0.96
Using morphine two days prior to death	1.76 (0.73–4.24)	0.21

(including the route and dosage) for dyspnea, both on admission and in the 48 h before death, did not significantly influence survival (HR: 0.015, 95% CI: 0.00–4.23; HR: 1.76, 95% CI: 0.73–4.24).

Discussion

To our knowledge, this study is one of the first to prospectively investigate the details of using morphine for dyspnea control in terminally ill cancer patients, particularly in patients with a Chinese culture. This study not only recorded the frequency of using morphine in the management of terminal dyspnea but also investigated its ethical acceptability and the satisfaction with quality of dyspnea control by both families and health care workers. Perhaps because of the misconceptions surrounding the medical role of opium-derived compounds, which originated with the opium wars in China in 1842, many patients and families with the background of Chinese culture still preferred to tolerate pain and/or dyspnea rather than use morphine. Poor pain and/or dyspnea control resulted in unnecessary deterioration of physical function and life quality, which unfortunately has been common in this patient group.[23] Furthermore, past experience in Taiwanese hospices has also shown that one of the controversies at the interface between general hospital wards and palliative care units involves the use of morphine in a terminally ill patient with dyspnea. When we have more evidence about the appropriate use of morphine for dyspnea control in this population, this may lead to better care for these patients, both in palliative care units and in general hospital wards.

Today, morphine is prescribed universally for pain management. In Taiwan, morphine use continues to be compromised by inadequate pain control education, misunderstandings about morphine tolerance, and concerns about side effects. Patients' attitudes, and social and cultural influences concerning the use of opioids, also must be considered. Pain is more likely to be endured in cultures where stoicism is valued, or when the expression of feelings is not encouraged, such as in a Taiwanese culture influenced by Confucian philosophy. Because of these beliefs, Taiwanese patients may avoid taking opioids, or may reduce their doses. Chiu et al.'s study in 1998 showed that opioid use is one of the major ethical dilemmas in palliative care.[24] Another important factor affecting pain control is the use of herbal drugs, in accordance with Taiwanese beliefs, which many patients fear might have adverse interactions with Western medication.

In recent decades, the government, with the cooperation of several health care professional groups, has identified and addressed concerns of health care professionals in prescribing opioids. The government also has informed health professionals about the legal requirements for the use of opioid drugs by providing many opportunities to discuss mutual concerns. A survey[25] in 2003 among cancer care professionals in Taiwan showed that only 14% still frequently have trouble deciding to use morphine for pain control; specifically, 86 of 136 patients (63.2%) had been prescribed morphine for their pain prior to the time of admission.

The use of morphine for dyspnea control is common in palliative care settings, but still arouses ethical controversy in Taiwan. In the present study, 40% of patients used morphine for dyspnea on admission and 54.5% had morphine two days prior to death. The fact that the proportion is so large indicates the importance of this problem. The reasons that morphine was not used in some cases, as discussed in weekly meetings, included: 1) misconceptions regarding opioids and worrying about its respiratory depressant actions and 2) concern about the effect on survival and the difficulty in distinguishing treatment from euthanasia. Medical staff also was reluctant to use morphine for patients with mild dyspnea. In the study, the frequency of using morphine for the group with mild dyspnea was less than the patients with moderate and severe dyspnea, both at the time of admission and prior to death (23.5% vs. 59.4%; 40.9% vs. 61.4%).

Clinically, when we choose morphine to control dyspnea, we clearly explain the reasons behind it and analyze the benefits and risks or burdens to clarify the difference between treatment and euthanasia and to prevent possible feelings of guilt among families or medical staff. After the explanation, the ethical acceptability of, and satisfaction with, using morphine to patients or their families are usually apparent from mutual interactions in the process of care.

In order to be more effective, the subcutaneous route of administration was used if oral administration was not feasible to maintain a therapeutic effect. A steady serum concentration obtained by the subcutaneous route compares to the intravenous route and further justifies the ethical adequacy.[11] We usually start giving morphine from 3 mg every 4 hours orally and titrate the dose to maximal efficacy or dose-limiting side effects.

All details are well explained and we hope to get consent from patients and families before doing so. However, in Oriental culture, it is common practice not to disclose the truth of the illness, especially to a terminally ill cancer patient, on the basis of non-maleficence. This mutual pretense prevails because both sides are unwilling to hurt each other and lack knowledge about how to communicate with each other. A previous study in Taiwan[24] showed that only one-quarter of patients admitted to hospice understood their terminal condition. Another 50% had families that were unsure of whether the patients knew of their terminal disease status, again probably due to mutual pretense. In the present study, some patients were not aware of the terminal nature of their disease, or had cognitive impairment, and the use of morphine for dyspnea was pursued only with the consent of family. Furthermore, due to changes in consciousness in the very terminal stage, more than half of morphine use (52.8%) was done with consent of families only prior to death.

Previous studies have shown that many symptoms of terminal cancer are aggravated in the last days.[2,7,8] Despite the fact that the mean dyspnea score increased significantly from 4.29 at admission to 4.94 two days prior to death, none of the patients or families, and only one of the medical staff, reported dissatisfaction with control of dyspnea. This can be explained in part by the recognition of family members and patients in Taiwan that aggravating symptoms are part of the natural process in dying, and by their belief in the ancient Tibetan Buddhist tradition, that the terminal dying process in humans is classified into five consecutive stages of disintegration with corresponding symptoms and signs.[26] They can observe the effects of morphine for controlling these aggravating symptoms and may also appreciate the full support and dedicated care from the palliative care team.

Some patients were not satisfied with the use of morphine, especially in the two days prior to death, and this deserves further investigation. Clinically we should continuously review the causes if the effect of morphine use for dyspnea control is not satisfactory. Titrating the dosage of morphine and selecting the appropriate routes based on the patient's situation are very important to improve the effects of morphine. Otherwise, total care, including pharmacological and non-pharmacological treatment, will be paramount in the management of dyspnea in palliative care. Furthermore, continuing communication with patients and their families is necessary to elevate the level of satisfaction.

Both the families and the medical staff always worry that if morphine is used for dyspnea control in terminally ill patients, this may shorten the patient's life.[15,16] The study used multiple Cox regression analysis to examine the influence of the following factors on survival: gender, age, primary cancer sites, metastasis sites, consciousness level, dyspnea score, and the use of morphine including the route and dosage. The result showed that using morphine for dyspnea, both on admission and in the 48 h before death, did not have a significant influence on the patients' survival. This finding also could be explained with reference to the "terminal common pathway" in cancer patients,[27,28] which may validate the ethical nature of using morphine in these terminal patients.

Certain caveats should be mentioned in relation to this study. First, other variables also may be related to the outcome of dyspnea control, such as other medications or chest care. These will be influential to the outcome of morphine use in the control of dyspnea. However, medical staff taking care of these patients are the most appropriate persons to monitor the effects of medications in the process of their care. Second, although patients in the

study came from everywhere in Taiwan, the generalizability of a unit study still should be a matter of concern.

In conclusion, the use of morphine for dyspnea control in the terminal phase of cancer patients was effective and ethically validated in the study. Good communication in order to clarify concerns and establish the goals of care can be helpful for the elevation of satisfaction in patients and families. Research efforts to find the most appropriate route and dosage of morphine for dyspnea, based on the patient's situation, remain worthwhile.

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