

Original Article

Sedation for Refractory Symptoms of Terminal Cancer Patients in Taiwan

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Abstract

This study assessed sedation in terminal cancer patients in terms of three characteristics: frequency; relationship to intractable symptoms; and the extent to which medical staff, family, and patients found sedation to be ethically acceptable and efficacious. Two hundred seventy-six consecutive patients, who were admitted to the palliative care unit of National Taiwan University Hospital in Taiwan between August 1998 and the end of May 1999, were enrolled. A recording form was completed every day. This included demographic data, pain and common symptom scores, and the use of sedation in the terminal phase. Seventy (27.9%) of 251 patients who died received sedation. Sedation was administered to relieve agitated delirium in 40 (57.1%), dyspnea in 16 (22.8%), severe pain in 7 (10%) and insomnia in 5 (7.2%). The drugs used for sedation were haloperidol in 35 (50%), midazolam in 17 (24.3%), and rapidly increasing dosage of morphine in 9 (12.9%). In fewer than half (42.9%) of the patients, sedation was with the consent of both patient and family, and half (50%) had the consent of family alone. The overwhelming majority of medical staff and family felt the decision to use terminal sedation was ethically acceptable. There was no significant difference in survival time between sedated and non-sedated patients (28.49 vs. 24.71 days, $t = -0.791$, $P = 0.430$). Positive ethical acceptability and higher satisfaction with symptom control with terminal sedation were found in both medical staff and family in this study. Further work is needed to find the most appropriate time of intervention and to improve management of refractory symptoms in dying patients. J Pain Symptom Manage 2001;21:467-472. © U.S. Cancer Pain Relief Committee, 2001.

Key Words

Sedation, terminal cancer, refractory symptom

Introduction

Nearly 30,000 people died of cancer in Taiwan in 1998, compared with 24,000 in 1994.¹

Unfortunately, the majority of cancer patients (including those in Taiwan) suffer physically, psychologically, and spiritually in their terminal stages. A study conducted at Memorial Sloan-Kettering Cancer Center showed that 17% out of 185 patients thought about committing suicide.² Another retrospective study by Coyle et al. revealed that 20% of 90 patients had suicidal thoughts.³ Support of patients

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with incurable cancer and alleviation of suffering is an essential task for medical professionals. Although there is total suffering in terminal cancer patients, physical symptoms such as pain, weakness, nausea, dyspnea, delirium, constipation, dysphasia, and edema often demand the most attention. These symptoms are often aggravated in the last days.^{4,5} Fortunately, there has been tremendous progress in symptom control in terminal cancer patients, especially in western countries. In Taiwan, we also have accumulated some experience in symptom control techniques. Nevertheless, there are some symptoms that cannot be adequately relieved.⁶ Sedation is usually considered to relieve these refractory symptoms.

The frequency of refractory symptoms in terminal cancer patients has been reported in many countries. The Italian National Cancer Institute found about 50% (63/120) of patients required sedation for symptom relief; among them were 33 patients with dyspnea, 31 patients with severe pain, 11 patients with delirium, and 5 patients with persistent vomiting.⁷ Fainsinger, in a retrospective study, found that 16 out of 100 terminal cancer patients needed sedation for symptom relief: 6 patients for pain and 10 patients for agitated delirium.⁵ The National Hospice Study in the U.S. reported that 25% of 269 terminal cancer patients had severe pain 2 days prior to death and 28% had severe dyspnea.⁸ Portenoy et al. showed that nearly one third of the terminally ill required heavy sedation to relieve pain.⁹

These studies suggest that sedation is required by a number of patients for intractable and devastating symptoms. Stone et al. showed that there was no difference in survival between sedated and non-sedated patients.¹⁰ However, the decision to sedate and to differentiate between natural death and voluntary active euthanasia, or physician-assisted suicide, has been a concern to health care workers.¹¹⁻¹⁴ We hope that decisions to sedate were within the framework of medical ethics, and used with appropriate timing and satisfactory effect, ensuring that patients could have a good death and that they were also morally acceptable to health care workers and family.¹⁵

The issue of sedation in the terminally ill also has drawn attention in Japan. Morita et al. reported that 69 out of 143 cancer patients received sedation to relieve symptoms, including

dyspnea, pain, malaise, agitation, and nausea. This study discussed the process of decision making, stressing the importance of sedation and communication with family members.¹⁶

In Taiwan, there have been no formal studies of sedation for control of terminal symptoms, although it has probably been practiced commonly for patients of Confucian culture. Thus, it is important to investigate its extent here. The aims of this study were to investigate the frequency of sedation in terminal cancer patients, its relationship with intractable symptoms, and to understand the ethical acceptability and satisfaction of symptom control among patients, family, and health care workers. This may lead to the development of a model of terminal care suitable for the care of terminal cancer patients in Taiwan.

Methods

Patients

Two hundred seventy-six consecutive patients admitted to the hospice and palliative care unit of National Taiwan University Hospital between August 1998 and the end of May 1999 were enrolled in the study. Eleven patients were lost to follow-up (due to transfer to other hospitals) and 14 were still alive at the end of the study.

Measurement

An assessment form, which was used daily, was designed by experienced specialists. It included demographic data, pain and dyspnea scores (on a 0-10 scale), and other common symptoms (scores: 0 = none; 1 = mild; 2 = moderate; 3 = severe). The form recorded the use of sedation, (including the consent for sedation), the medication of choice, (increased dosage of morphine; midazolam, diazepam or other benzodiazepine; haloperidol or another neuroleptic; or a barbiturate), date of administration, reasons for administration (pain, dyspnea, malaise, agitation, nausea, vomiting, depression, anorexia, insomnia not predominately with other intractable symptoms), route of administration (oral, subcutaneous, intravenous, intramuscular, rectal), frequency, desirable effects, and untoward effects. Ethical acceptability and satisfaction with symptom control of medical staff, family, and patients were also recorded.

Methods

The prevalence of symptoms and use of sedation for symptoms control were recorded daily by the same staff members. They assessed and recorded the presence or absence of symptoms, their severity, and the use of sedation. These data were discussed in weekly team meetings at the time of admission and 48 hours prior to death. A refractory terminal cancer symptom was defined as one incapable of adequate relief, which caused severe suffering, and was unlikely to lessen within a short time. Sedation was defined as a medical procedure to palliative patients' symptoms by intentionally making their consciousness unclear.

Statistical Analysis

Data management and statistical analysis was performed using SPSS 8.0 statistical software. Frequency distributions were used to describe the demographic data and the distribution of each variable. Mean values and standard deviations were used to analyze the severity of each symptom. The chi-square test was used to compare the differences between frequency of terminal sedation and severity of symptoms. Finally, the *t*-test was used to compare symptom severity of symptom and the survival between sedated and non-sedated patients. A *P* value less than 0.05 was considered statistically significant.

Results

There were 54% men and 46% women (Table 1). One-half of the 276 patients (51.1%) were older than 65 years, and only six patients were younger than 18 years. The primary sites of cancer were lung (20.7%), liver (20.3%), colorectal (9.8%) and head and neck (5.8%); 227 of 276 patients (82.2%) had metastasis.

Table 2 shows details of sedation for symptom control. Seventy (27.9%) of 251 patients who died received sedation: 40 (57.1%) for agitated delirium, 16 (22.8%) for dyspnea, 7 (10%) for severe pain and 5 (7.2%) for insomnia. Two patients (2.9%) received sedation for pruritus. The medication used was haloperidol in 35 (50%), midazolam in 17 (24.3%), and rapidly increasing dosage of morphine in 9 (12.9%). Administration routes were: oral in 35 (50%), subcutaneous in 30 (42.9%), and intravenous in 5 (7.1%). More than half (52.9%) of sedated patients received medication intermittently and

Table 1
Demographic Characteristics of Patients

Variables	No. of patients	%
Sex		
Male	149	54.0
Female	127	46.0
Age group		
≤12	4	1.4
13–18	2	0.7
19–35	13	4.7
36–50	36	13.0
51–64	80	29.1
≥65	141	51.1
Survival days		
≤3	41	14.9
4–7	46	16.7
7–30	109	39.5
≥31	55	19.9
Mean ± SD = 23.49 ± 31.76 days		
Still alive	14	5.1
Missing	11	4.0
Primary sites of cancer		
Lung	57	20.7
Liver	56	20.3
Colorectal	27	9.8
ENT	16	5.8
Pancreas	13	4.7
Stomach	13	4.7
Cervical/Uterine	12	4.3
Uncertain	10	3.6
Breast	9	3.3
Other	63	22.8
Total	276	100.0

nearly 37.1% received medication continuously. One-tenth of sedated patients progressed to continuous sedation from intermittent use. Fewer than half (42.9%) of those sedated had had the informed consent of both patients and the family; 50% of the sedation (*n* = 35) was only with consent of proxy family. Almost all of the patients who were sedated without verbal consent were cognitively impaired. Two out of six children received sedation, and one of them could agree with the use of sedation.

Table 3 shows that in most cases sedation was ethically acceptable to medical staff (95.7%). However, only 71.4% of the medical staff were satisfied with the effectiveness of symptom control. Nearly 90% of the families thought it was right to use sedation, but 67.1% thought that the outcome of sedation was satisfactory and only half (52.9%) of the patients who could respond themselves were satisfied with the effect of sedation.

Both at the time of admission and at 48 hours before death, those sedated had higher mean scores for pain, dyspnea, and delirium

Table 2
Content of Sedation for Symptom Control

Variables	No. of patients	%
Sedation		
Sedated	70	27.9
Non-sedated	181	72.1
Refractory Symptoms		
Agitated delirium	40	57.1
Dyspnea	16	22.8
Pain	7	10.0
Insomnia not predominantly with intractable symptoms	5	7.2
Severe itching	2	2.9
Route		
Oral	35	50.0
Subcutaneous	30	42.9
Intravenous	5	7.1
Medication for Sedation		
Haloperidol	35	50.0
Midazolam	17	24.3
Morphine, rapidly increasing dose	9	12.9
Other benzodiazepines	7	10.0
Chlorpromazine	2	2.8
Frequency		
Intermittently	37	52.9
Continuously	26	37.1
Intermittently continuously	7	10.0
Consent		
Family only	35	50.0
Patient and family	30	42.9
Patient only	5	7.1
Total patients	251	100.0

(Table 4). There were significant differences among those with dyspnea at admission, delirium at admission, and delirium two days prior to death ($t = -2.05$, $P < 0.05$; $t = -2.55$, $P < 0.05$; $t = -4.25$, $P < 0.001$). There was no difference between frequency of sedation and the primary sites of cancer.

The mean survival times of 28.5 days for sedated and 24.7 days for non-sedated patients were not statistically different ($t = -0.79$, $p = 0.43$) (Table 5). The mean survival time was 12.6 ± 19.6 days from starting sedation to the time of death, with a median of 5 days. The mean survival was 4.3 ± 8.6 days from the last use of sedation to death, and the median was 2 days. Sedation was usually discontinued at the very end of life, because many actively dying patients lost consciousness gradually and some devastating symptoms, such as agitation or severe pain, might lessen at that time.

Discussion

This prospective study not only recorded the frequency of sedation in the management of

Table 3
Satisfaction and Ethical Acceptability of Sedation

Variable	No. of patients	%
Ethical acceptability of medical staff		
Should provide sedation	67	95.7
Might be right	3	4.3
Satisfaction of medical staff		
Yes	50	71.4
Fair	14	20.0
No	6	8.6
Ethical acceptability of family		
Should provide sedation	62	88.6
Might be right	3	4.3
Unavailable	5	7.1
Satisfaction of family		
Yes	47	67.1
Fair	14	20.0
No	3	4.3
Unavailable	6	8.6
Satisfaction of patient		
Yes	37	52.9
Fair	7	10.0
No	3	4.3
Unavailable	23	32.8
Total sedated patients	70	100.0

terminal symptoms but also investigated its ethical acceptability and the satisfaction with the quality of symptom control by both family and health care workers. The reasons for sedation were clearly explained to the patients (if possible) and family to clarify its difference from euthanasia and to relieve any future sense of guilt. The ethical acceptability of, and satisfaction with, sedation in patients or their families were usually apparent in the opinions of health care workers, based on observations and from mutual interactions in the process of care.

In this study, the frequency of sedation was 27.9% (70/251), lower than the 52% reported in the study by the Italian National Institute⁷ and the 48.3% reported by Morita et al.¹⁶ We defined sedation as the use of agents to relieve refractory symptoms causing intolerable suffering which were otherwise incapable of adequate relief within an acceptable time. Those who did not meet the criteria and received some medication for common symptoms (such as haloperidol to improve nausea and vomiting) were not included in the study.

Agitated delirium (57.1%) was the most frequent symptom requiring sedation in the study. Ventafridda and Fainsinger reported that 10% to 20% of delirious patients needed significant sedation to relieve suffering.^{5,7} In delirious patients, the underlying cause was

Table 4
Symptoms of Sedated ($n = 70$) and Non-Sedated ($n = 206$) Patients

	Sedated (mean \pm SD)	Non-Sedated (mean \pm SD)	<i>t</i> value	<i>P</i> value
Pain, admission	3.79 \pm 2.78	3.54 \pm 2.67	-0.674	0.501
Pain, 2 days before death	2.53 \pm 2.41	2.14 \pm 2.26	-1.107	0.270
Dyspnea, admission	3.26 \pm 3.15	2.44 \pm 2.75	-2.054	0.040 ^a
Dyspnea, 2 days before death	2.97 \pm 2.93	2.85 \pm 2.72	-0.286	0.775
Delirium, admission	1.40 \pm 1.01	1.05 \pm 0.94	-2.547	0.010 ^a
Delirium, 2 days before death	1.80 \pm 0.98	1.14 \pm 1.01	-4.246	0.000 ^a

^aPain score: 0~10; dyspnea score: 0~10; delirium score: 0~3.

treated first with provision of a comfortable environment and psychological support. Nevertheless, up to 40 patients required sedation for intractable terminal stage agitation.

Dyspnea was the second commonest symptom needing sedation (22.8%). Despite the management of dyspnea by providing psychological support, oxygen, morphine, or steroid to relieve discomfort, 16 patients required sedation to relieve suffering.

The majority of the terminal cancer pain could be relieved under the guidelines of cancer pain control proposed by the World Health Organization.¹⁷ However, rapidly increasing doses of morphine or midazolam were prescribed for 7 patients for severe pain. Continuous midazolam was used in two patients for intractable pruritus.

Sedation in terminal cancer is controversial in Taiwan. Many health care workers engaged in palliative care believe that by promotion of psychological power the suffering of physical symptoms can be overcome. Some regard suffering as an essential part of life, and are opposed to the application of sedation that diminishes the gain of psychological and spiritual enrichment. Also, many Taiwanese are Buddhist, and believe that good death can only be obtained if consciousness is kept clear near the end of life. Additionally, some people

fail to appreciate the difference between sedation for management of symptoms and euthanasia.

Other groups of health care workers argue that sedation should be undertaken more aggressively if the intention is to relieve suffering. Staff is ethically allowed to use sedatives from the perspective of the principle of double effect. Besides, it would be very difficult for a terminal patient with severe sufferings to enrich their mind. Consensus, reached after long discussion, states that sedation should be carried out only with the intention of relieving suffering in terminally ill patients with cautious selection of medication, dosage, and routes of administration. Sedation is considered best used only at night initially so that patients can have more sleep and get more energy in the daytime to receive the team care promoting psycho-spiritual development. Under these guidelines, in this study, half (50%) of the sedated patients received sedation orally, 49.2% by the subcutaneous route, and only 5 patients intravenously. Midazolam (2.5 mg) was usually used intermittently in the beginning, or started from 0.02 mg/kg/hr if continuous use was indicated. Continued communication is essential to ensure informed consent from either patient or proxy family before the use of sedation. Although continuous sedation might be

Table 5
Survival of Sedated ($n = 65$) and Non-Sedated ($n = 162$) Patients

	Sedated (mean \pm SD)	Non-Sedated (mean \pm SD)	<i>t</i> value	<i>P</i> value
Survival from date of admission ^a (days)	28.49 \pm 36.37	24.71 \pm 30.90	-0.791	0.430
Survival from start of sedation ^a (days)	12.62 \pm 19.59	—	—	—
Median 5	—	—	—	—
Survival from last time of sedation ^a (days)	4.30 \pm 8.61	—	—	—
Median 2	—	—	—	—

^aOnly patients admitted more than 2 days.

necessary for controlling refractory symptoms, an intermittent approach is often preferable in our circumstance. Intermittent uses of sedation also enable medical staff and family members to confirm the effect and necessity of sedation. In our study, about one-half of the sedation patients received sedation intermittently until natural death came.

The majority of medical staff and family were satisfied with the effect of sedation. No significant untoward effects were observed. Only four patients appeared to suffer drug-induced delirium and no respiratory suppression was noticed in the sedated patients. To both medical staff and family, the use of sedation was ethically acceptable. There was also no difference in survival time between the sedated and non-sedated groups ($P = 0.430$).

From this experience, we recognized that the use of sedation is effective in reducing the suffering of Taiwanese patients with terminal cancer. For those who did not respond well to terminal sedation (20/70), investigations should be directed at improving medication and communication between health care workers, patients, and their families. Further studies also are needed to make the outcome of sedation better and to find the method and most appropriate time to sedate the imminently dying with refractory symptoms.

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