

Sedation for terminally ill cancer patients

A multicenter retrospective cohort study in South Korea

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Abstract

Sedation therapy is a potential solution to providing relief from refractory symptoms at end of life. The aim of this study was to investigate actual sedation practice and physician characteristics associated with the use of sedation for terminally ill cancer patients in South Korea.

A retrospective review was conducted on consecutive patients who had died from cancer at seven tertiary medical centers between January 2010 and October 2015. The use of sedation was defined as the administration of sedative agents to relieve intolerable symptoms within the last 2 weeks preceding death. Patients and physician characteristics and information on the use of sedation were collected.

A total of 8309 patients were included in the study. Sedatives were administered in 1334 patients (16.1%) for the following indications: delirium in 39.3%, intractable pain in 23.1%, and dyspnea in 21.9%. Median duration of sedation from initiation to death was 3 days. The use of sedation depended on physician specialty and experience. Family physicians used sedation most often (57.6%), followed by medical oncologists (13.9%), other internists (10.7%), and surgical oncologists (9.4%). The use of sedation was highest for physicians with >5 to 10 years practice experience (22.1%) and lowest for those in practice for 5 years or less (10.2%). The proportion of patients receiving sedation also varied markedly across participating institutions (range, 7.0%–49.7%).

This large cohort study provides insight into sedation practice for terminally ill cancer patients in South Korea. Our study shows that the use of sedation depends on physician background and institution. A nation-wide guidelines and continued education on end-of-life sedation are required in South Korea.

Abbreviation: SPSS = Statistical Package for the Social Sciences.

Keywords: cancer, death, physician, sedation

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1. Introduction

Terminally ill cancer patients commonly exhibit severe physical and psychological symptoms^[1–3] and adequate symptom control is the core of palliative care.^[4,5] Despite ongoing efforts to alleviate symptoms, physicians occasionally fail to relieve patient suffering.^[6–9] Palliative sedation therapy is a potential solution to provide relief from these refractory symptoms. Use of sedation is distinct from Euthanasia^[10] and does not hasten death in patients with terminal cancer.^[11,12] Several guidelines provide appropriate indications for the use of sedation and detail its clinical implications.^[1,13,14]

The rate of use of sedation for patients with terminal cancer varies in western countries from 10% to 66.7% and depends on culture, country, subjects, and care setting.^[12,15,16] Although many studies have evaluated sedation practice, few have been undertaken in Asia, where family members tend to be deeply involved in health-care decision making, even if patients are fully competent.^[17] Thus, we considered significant differences may exist in the use of sedation therapy. A previous Japanese study reported that palliative sedation was used in 50.3% of patients in a palliative care unit.^[18] However, the study sample size ($n=124$) was too small to assess real practice patterns. Previously, we reported that the sedation rate in dying cancer patients was only 2%,^[19] but this study was limited by its single cancer center design and exclusion of episodic use of sedatives for symptom relief.

The aim of the present study was to investigate actual sedation practice in South Korea, including the percentage of sedated patients, type of sedation (continuous or intermittent), drugs, indications, and to identify physician-associated factors related to the use of sedation.

2. Methods

2.1. Patients

We conducted a review of consecutive patients who died of advanced cancer at seven tertiary medical centers in South Korea between January 2010 and October 2015. Computer archived medical records were used to obtain data for the analysis. The use of sedation at end of life was defined as the administration of intravenous or oral sedative medication to relieve intolerable symptoms within the last 2 weeks of life. Sedative agents included benzodiazepines (midazolam, diazepam, lorazepam, and clonazepam), barbiturates (phenobarbital and thiopental), and propofol. The use of sedatives for an endoscopic procedure, insomnia, anxiety, or seizure control was excluded. Sedation was classified as either continuous or intermittent. Continuous sedation involves the uninterrupted use of sedation until death, whereas intermittent sedation is applied for short-term symptomatic relief with return of consciousness in between. This retrospective study was approved by the institutional review board at each participating center. The requirement for informed patient consent was waived because our study posed minimal risk to patients and obtaining consent was impracticable.

2.2. Data collection

Data regarding

- (1) clinical characteristics of patients: age, sex, and cancer type,
- (2) details of sedation: commencement date, indication for use, specific drugs used, type of sedation, and
- (3) physician characteristics: specialty, duration of practice, and affiliation were collected.

Duration of sedation was measured in days from the first dose of sedatives until the time of death.

2.3. Statistical analysis

Descriptive data are presented as numbers (%) or mean (standard deviations). Comparisons of baseline characteristics between sedated patients and non-sedated patients were performed using Student *t* test for continuous variables and the chi-square test for categorical variables. Two-sided *P* values < .05 were considered statistically significant. The analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 21.0; SPSS Software, IBM Corp., Armonk, NY).

3. Results

3.1. Patient characteristics and sedation rates

A total of 8309 patients were included in the study. Mean patient age was 61.6 (± 13.1) years and 62.5% were male. The most common cancer was gastrointestinal (40.5%) followed by lung cancer (24.1%). End of life care was mainly performed by hematology or oncology specialists (91.4%). Overall, 1334 patients (16.1%) received sedation. Sedations rates varied according to cancer type (range, 8.3%–19.4%); the use of

sedation was highest with lung cancer. The use of sedation varied according to gender and the area of specialization of the treating physician. Male patients received sedation more often than female patients (16.8% vs. 14.8%, $P = .017$). Sedation rates were significantly different depending on physician specialty; family physicians used sedation therapy most often (57.6%), followed by hematologists/medical oncologists (13.9%), other internists (10.7%), and surgical oncologists (9.4%). Career duration also influenced the use of sedation, with the highest use by physicians with >5 to 10 years of experience (22.1%) and lowest for those with 5 years or less (10.2%). In addition, the proportion of sedated patients varied markedly between participating institutions (range, 7.0%–49.7%). The characteristics of sedated and non-sedated patients are summarized in Table 1.

3.2. Clinical features of sedation

Indications for sedation included delirium ($n = 524$, 39.3%), pain ($n = 308$, 23.1%), dyspnea ($n = 292$, 21.9%), and other reasons ($n = 210$, 15.7%) (Table 2). Median duration of sedation from initiation to death was 3 days (range, 1–36 days). Lorazepam was most frequently used for sedation (34.8%), followed by midazolam (28.9%) and diazepam (18.6%). Intermittent sedation until death was used more often than continuous sedation (61.8% vs. 38.2%).

4. Discussion

This study describes current sedation practice in terminal cancer patients in South Korea. To the best of our knowledge, this study included the largest cohort ($n = 8309$) of terminally ill cancer patients investigated to date. Another strength of the present study is that it encompassed different clinical settings providing end of life care for cancer patients, including inpatient hospice unit and medical oncology, internal medicine, and surgical wards. In South Korea, about 90% of patients die in hospitals, although home is considered to be the ideal place for end of life care.^[20] The percentage of patients that received sedation in our cohort was 16.1%, which is lower than previously reported. One of the largest studies on this topic from Austria ($n = 2414$) reported that 21% of patients in palliative care units received sedation for refractory symptoms.^[21] A systematic review of 1807 patients including 10 studies by Maltoni et al^[12] reported a sedation rate of 34.4%, but there was a large inter-study variation (range, 14.6%–66.7%).

Our data showed that end of life care in Korean cancer patients is usually provided by medical oncologists who were engaged in active cancer treatment for their patients. Lack of knowledge, negative perceptions towards hospice care, and insufficient facilities hinder referral of terminal cancer patients to specialist palliative care units.^[22] As a result, only 14% of terminal cancer patients were estimated to receive hospice and palliative services in South Korea.^[23] Interestingly, in the present study, physician background, training, and experience were found to influence decision making regarding sedation therapy at end of life. No clinical practice guidelines on palliative sedation have been issued in Korea, and this lack of a national consensus has resulted in considerable variation in practice among treating physicians. The high rate of sedation (57.6%) practiced by family physicians may be related to the fact that they usually manage cancer patients in the palliative care setting. In contrast, surgical oncologists, who usually provide curative anticancer treatment, used sedation least frequently. These findings demonstrate nation-wide recommen-

Table 1**Patient characteristics and comparison between sedated and non-sedated patients.**

Variables	Total(n = 8309)	Sedated (n = 1334)	Non-sedated (n = 6975)	P value
Age, years				.547
Mean ($\pm$ SD)	61.6 ($\pm$ 13.1)	61.8 ($\pm$ 12.7)	61.6 ($\pm$ 13.2)	
Sex				.017
Male	5195	872 (16.8%)	4323 (83.2%)	
Female	3114	462 (14.8%)	2652 (85.2%)	
Primary tumor				<.001
Gastrointestinal	3376	622 (18.4%)	2754 (81.6%)	
Lung	2001	389 (19.4%)	1612 (80.6%)	
Genitourinary	408	69 (16.9%)	339 (83.1%)	
Breast	367	62 (16.9%)	305 (83.1%)	
Head and neck	261	34 (13.0%)	227 (87.0%)	
Others*	1896	158 (8.3%)	1738 (91.7%)	
Physician's specialty				<.001
Hematology/medical oncology	7598	1056 (13.9%)	6542 (86.1%)	
Internal medicine except H/MO	215	23 (10.7%)	192 (89.3%)	
Family medicine	432	249 (54.6%)	183 (42.4%)	
Surgery	64	6 (9.4%)	58 (90.6%)	
Practice duration of physician†				<.001
$\leq$ 5 years	461	47 (10.2%)	414 (89.8%)	
>5–10 years	2982	658 (22.1%)	2324 (77.9%)	
>10–15 years	1645	237 (14.4%)	1408 (85.6%)	
>15 years	3189	392 (12.3%)	2797 (87.7%)	
Institution				<.001
A	2211	207 (9.4%)	2004 (90.6%)	
B	2700	189 (7.0%)	2511 (93.0%)	
C	731	88 (12.0%)	643 (88.0%)	
D	789	164 (20.8%)	625 (79.2%)	
E	338	126 (37.3%)	212 (62.7%)	
F	539	268 (49.7%)	271 (50.3%)	
G	1001	292 (29.2%)	709 (70.8%)	

H = hematology, MO = medical oncology, SD = standard deviation.

* Others include hepatobiliary cancers ($n=1049$), gynecologic cancer ($n=241$), hematologic malignancies ($n=232$), cancer of unknown primary site ($n=99$), soft tissue sarcomas ($n=84$), skin cancers ($n=51$), primary bone cancers ($n=36$), primary central nervous system tumors ($n=35$), thyroid cancer ($n=21$), neuroendocrine tumors ($n=16$), and unspecified ($n=32$).

† Information about the practice duration of physician was not available in 32 patients.

dations are required to provide physicians with a framework for decision-making and clinical application.

Benzodiazepines are the most commonly used medications for sedation; among the benzodiazepine class of drugs, midazolam is most frequently prescribed and considered a drug of first choice.^[6,24] Midazolam has advantages over other benzodiazepines because of its rapid onset, short elimination half-life, and

easy titration.^[25,26] In the present study, lorazepam was more often administered than midazolam, and diazepam (another benzodiazepine) was commonly used, which indicates that the choice of drug for palliative sedation also depended on physician experience and preference. Delirium, pain, and dyspnea were the main refractory symptoms that led to the use of sedation. Consistent with previous reports,^[12,21] delirium was the most common indication for sedation in our study. The median duration of sedation in the present study was 3 days, which is similar to those reported in previous studies.^[6,18,27]

Our study has several limitations due to its retrospective design. First, we did not acquire detailed information about sedation, including the level of sedation, use of concurrent drugs, drug dosage, family wishes, and decision-making processes. Second, no information was available regarding physician attitude and level of knowledge regarding palliative sedation. To reduce bias, prospective, multicenter studies are required, and a standardized format should be used to record details of sedation practice.

In conclusion, this large cohort study provides insight into the current sedation practice in terminally ill cancer patients in South Korea. It reveals wide variations in the rate of use of sedation that depend on physician background, training, and experience. We recommend the introduction of nation-wide guidelines regarding indications and optimization of palliative sedation and continued education on its use in South Korea.

Table 2**Sedation characteristics.**

Characteristics	No. (%)
Indication	
Delirium	524 (39.3%)
Pain	308 (23.1%)
Dyspnea	292 (21.9%)
Others	210 (15.7%)
Duration (days)	
Median	3
Range	1–36
Sedative drugs	
Lorazepam	438 (32.8%)
Midazolam	385 (28.9%)
Diazepam	248 (18.6%)
Propofol	1 (0.1%)
Others	262 (19.6%)
Types	
Intermittent	825 (61.8%)
Continuous	509 (38.2%)

Author contributions

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References

- [1] Cherny NI. ESMO Guidelines Working Group. ESMO Clinical Practice Guidelines for the management of refractory symptoms at the end of life and the use of palliative sedation. *Ann Oncol* 2014;25(Suppl 3):iii143–52.
- [2] Barbera L, Seow H, Howell D, et al. Symptom burden and performance status in a population-based cohort of ambulatory cancer patients. *Cancer* 2010;116:5767–76.
- [3] Baker TA, Krok-Schoen JL, McMillan SC. Identifying factors of psychological distress on the experience of pain and symptom management among cancer patients. *BMC Psychol* 2016;4:52.
- [4] Grunberg SM. New directions in supportive care. *Support Care Cancer* 2005;13:135–7.
- [5] Tai SY, Lee CY, Wu CY, et al. Symptom severity of patients with advanced cancer in palliative care unit: longitudinal assessments of symptoms improvement. *BMC Palliat Care* 2016;15:32.
- [6] Beller EM, van Driel ML, McGregor L, et al. Palliative pharmacological sedation for terminally ill adults. *Cochrane Database Syst Rev* 2015;1:CD010206.
- [7] Claessens P, Menten J, Schotsmans P, et al. Palliative sedation: a review of the research literature. *J Pain Symptom Manage* 2008;36:310–33.
- [8] Anquinet L, Rietjens J, van der Heide A, et al. Physicians' experiences and perspectives regarding the use of continuous sedation until death for cancer patients in the context of psychological and existential suffering at the end of life. *Psychooncology* 2014;23:539–46.
- [9] Morita T, Imai K, Yokomichi N, et al. Continuous deep sedation: a proposal for performing more rigorous empirical research. *J Pain Symptom Manage* 2017;53:146–52.
- [10] ten Have H, Welie JV. Palliative sedation versus euthanasia: an ethical assessment. *J Pain Symptom Manage* 2014;47:123–36.
- [11] Maeda I, Morita T, Yamaguchi T, et al. Effect of continuous deep sedation on survival in patients with advanced cancer (J-Proval): a propensity score-weighted analysis of a prospective cohort study. *Lancet Oncol* 2016;17:115–22.
- [12] Maltoni M, Scarpi E, Rosati M, et al. Palliative sedation in end-of-life care and survival: a systematic review. *J Clin Oncol* 2012;30:1378–83.
- [13] Gurschick L, Mayer DK, Hanson LC. Palliative sedation: an analysis of international guidelines and position statements. *Am J Hosp Palliat Care* 2015;32:660–71.
- [14] Abarshi E, Rietjens J, Caraceni A, et al. Towards a standardised approach for evaluating guidelines and guidance documents on palliative sedation: study protocol. *BMC Palliat Care* 2014;13:34.
- [15] Quill TE, Lo B, Brock DW. Palliative options of last resort: a comparison of voluntarily stopping eating and drinking, terminal sedation, physician-assisted suicide, and voluntary active euthanasia. *JAMA* 1997;278:2099–104.
- [16] Maltoni M, Scarpi E, Nanni O. Palliative sedation in end-of-life care. *Curr Opin Oncol* 2013;25:360–7.
- [17] Lee SK, Knobf MT. Family involvement for breast cancer decision making among Chinese-American women. *Psychooncology* 2016;25:1493–9.
- [18] Kohara H, Ueoka H, Takeyama H, et al. Sedation for terminally ill patients with cancer with uncontrollable physical distress. *J Palliat Med* 2005;8:20–5.
- [19] Haa Na S, An Na L, Un Suk L, et al. Palliative sedation: experience in a Tertiary Center in Korea. *Korean J Med* 2013;2013:267.
- [20] Cohen J, Pivodic L, Miccinesi G, et al. International study of the place of death of people with cancer: a population-level comparison of 14 countries across 4 continents using death certificate data. *Br J Cancer* 2015;113:1397–404.
- [21] Schur S, Weixler D, Gabl C, et al. Sedation at the end of life—a nationwide study in palliative care units in Austria. *BMC Palliat Care* 2016;15:50.
- [22] Jho HJ, Chang YJ, Song HY, et al. Perceived timeliness of referral to hospice palliative care among bereaved family members in Korea. *Support Care Cancer* 2015;23:2805–11.
- [23] Shim HY, Chang YJ, Kawk KS, et al. Do Korean doctors think a palliative consultation team would be helpful to their terminal cancer patients? *Cancer Res Treat* 2017;49:437–45.
- [24] de Graeff A, Dean M. Palliative sedation therapy in the last weeks of life: a literature review and recommendations for standards. *J Palliat Med* 2007;10:67–85.
- [25] Dean MM, Cellarius V, Henry B, et al. Framework for continuous palliative sedation therapy in Canada. *J Palliat Med* 2012;15:870–9.
- [26] Nogueira FL, Sakata RK. Palliative sedation of terminally ill patients. *Rev Bras Anestesiol* 2012;62:580–92.
- [27] Maltoni M, Pittureri C, Scarpi E, et al. Palliative sedation therapy does not hasten death: results from a prospective multicenter study. *Ann Oncol* 2009;20:1163–9.