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Brief Communication

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Characteristics Associated with Survival in Patients Receiving Continuous Deep Sedation in a Hospice Care Unit

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Continuous deep sedation (CDS) is an extreme form of palliative sedation to relieve refractory symptoms at the end of life. In this study, we shared our experiences with CDS and examined the clinical characteristics associated with survival in patients with terminal cancer who received CDS. We conducted a chart audit of 106 consecutive patients with terminal cancer who received CDS at a single hospice care unit between January 2014 and December 2016. Survival was defined as the first day of admission to the date of death. The associations between clinical characteristics and survival were presented as hazard ratios and 95% confidence intervals using a Cox proportional hazard model. The mean age of participants was 65.2 years, and 33.0% (n=35) were women. Diazepam was the most commonly administered drug, and haloperidol or lorazepam were also used if needed. One sedative was enough for a majority of the patients. Stepwise multivariate analysis identified poor functioning, a high Palliative Prognostic Index score, hyperbilirubinemia, high serum ferritin levels, and a low number of sedatives as independent poor prognostic factors. Our experiences and findings are expected to be helpful for shared decision-making and further research on palliative sedation.

Key Words: Deep sedation, Hospices, Survival analysis, Terminal care

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INTRODUCTION

Palliative sedation is a method for decreasing awareness using strong sedatives to relieve severe pain or end-of-life symptoms that cannot be controlled with other treatments in terminally ill patients [1]. There are not yet clear clinical protocols for palliative sedation, and the protocols that are performed often vary by country, research group, or individual physician [2]. There have been multiple recent studies and accounts from different countries demonstrating such variation [3-8], but very few studies have focused on continuous deep sedation (CDS), the strongest form of palliative sedation.

In South Korea, palliative sedation was only recently added to the Clinical Practice Guideline for Care in the Last Days of Life, which is a guideline certified by the Korean Society for Hospice and Palliative Care, at recommendation level D [9]. A South Korean study on palliative sedation examined indications and the duration of sedation in 1,334 patients at a tertiary hospital who received sedation treatment in the last 2 weeks of their lives, but it mainly focused on the characteristics of medical personnel who administered sedation treatment rather than on the treatment itself [10]. Another South Korean study prospectively observed treatment indications, medications, and survival using data from 89 patients who received seda-

tion treatment at a single hospice ward. However, the study examined the differences between intermittent and continuous sedation methods rather than the depth of sedation [11].

The aim of this study was to share our experiences administering CDS to terminal cancer patients at an in-patient hospice unit, analyze the factors related to the survival of patients who received CDS, and provide data for future decision-making and follow-up studies.

METHODS

This study used data from 106 terminal cancer patients at a single hospice care facility for whom CDS had been administered before their deaths from January 1, 2014, to December 31, 2016. CDS was defined as a maintained state of decreased consciousness to a stupor or unconsciousness caused by sedatives leading up to a patient's death [12]. This study obtained institutional review board approval from the authors' affiliated institution (GBIRB2019-309), and a retrospective review of medical records was conducted.

Sedation was administered according to a consistent pattern since patients' attending physicians did not change, and the eligibility criteria for study participants were as follows. First, patients must have had severe symptoms that did not respond to other treatment options. Refractory pain was identified after considering not only medications but also treatment choices such as palliative radiotherapy and nerve blocks. Delirium, including delirium caused by imbalances in electrolytes and medications, and dyspnea caused by conditions other than the progression of cancer, such as asthma, pneumonia, pleural effusion, pulmonary edema, and anxiety, were also considered. Symptoms were considered refractory when there was no response within a few days of administering treatment, based on the National Comprehensive Cancer Network clinical guidelines (nccn.org/guidelines/category_3).

Second, the decision to administer CDS was made through a strict decision-making process that involved a hospice team composed of medical personnel across diverse positions, family members, and the patient when possible, and all decisions were made verbally. Third, the main drug used to induce sedation was diazepam, beginning with routine 10 mg injections throughout the day until an awareness level below a stupor was reached [13] by doubling the dose every 8 hours. If the patient did not reach an awareness level below a stupor using diazepam alone within 24 hours, another type of sedative was routinely injected in addition to diazepam. The dose titration method was the same as that of diazepam.

The following data were collected at the time of hospitalization: age, sex, primary cancer, function (Eastern Cooperative Oncology Group Performance Status [ECOG-PS] score ranging from 0 to 4) [14], Prognostic Palliative Index (PPI) score, the symptom that necessitated CDS, and the medication used to administer CDS. A blood test was conducted on the day of hospitalization according to existing protocols, and a follow-up test was conducted every week. When the patient was transferred from another department in the hospital and had received a blood test within the past week, a blood test was conducted after several days. The start of the survival period in this study was not the initiation of CDS but rather the beginning of in-patient hospice care, which was operationalized as the date of the first blood test in this ward. Values beginning at that point in time were used.

Statistical analysis was conducted using STATA SE 9 (STATA Corp., College Station, TX, USA). Differences in the average survival time according to participant characteristics were identified using the Kaplan-Meier survival analysis method, and Cox proportional hazard regression analysis was conducted to evaluate the factors that influenced the survival time of study participants. Using backward elimination, the final sets of variables related to the prognosis of patients were extracted, and the hazard ratio and 95% confidence interval of the variables were calculated. A P-value <0.05 was considered to indicate statistical significance for all analysis results.

RESULTS

The general characteristics of the participants are shown in Supplementary Table 1. The average age of the participants was 65.2 years. A total of 33.0% of the participants were female, and most of the participants had liver, bile duct, or pancreatic cancer (n=29). Patients were most often administered diazepam, followed by haloperidol (45.3%) and lorazepam (11.3%). Midazolam was rarely used. The average dose of each drug at the point of reaching CDS was 33.8 mg for diaz-

epam, 8.3 mg for lorazepam, and 6.0 mg for haloperidol. The most frequent indication was pain (n=44, 41.5%), followed by delirium/anxiety (39.6%) and dyspnea (17.9%).

The differences in survival time according to the characteristics of participants are shown in Table 1. Significantly longer survival times were found in those who received a PPI score of 6 or below compared to those who received a score above 6 (13 days vs. 7 days; P=0.023), those who did not have hyperbilirubinemia compared to those who did (13 days vs. 9 days; P=0.008), those who had low ferritin levels compared to those who had high ferritin levels (13.5 days vs. 9 days; P=0.006), and those who were administered lorazepam compared to those who were not (21.5 days vs. 10.5 days; P=0.048). The difference in survival time according to the number of drugs administered to induce CDS was also statistically significant (P=0.035).

The likelihood of a poor prognosis for those with an ECOG-PS of 4 was 1.78 times higher than in those whose score was lower than 4, and a poor prognosis was 2.18 times more likely for those with a PPI score above 6 than for those with a PPI score of 6 or below. The likelihood of a poor prognosis for those who had hyperbilirubinemia was 2.04 times higher than for those who did not, and a poor prognosis was 2.28 times more likely for those who had high ferritin levels than for those who did not. The number of sedatives administered and the prognosis had a positive correlation, in which an increase in the number of sedatives administered corresponded to an increase in the likelihood of a good prognosis by 1.4 times (Table 2).

Table 1. Median Survival Time According to Patients' Characteristics upon Admission (N=106).

Variables	n	MST, days	95% CI	P†
ECOG-PS				
1~3	75	13	11~18	0.071
4	31	7	4~12	
PPI score				
≤6	60	13	11~19	0.023
>6	40	9	4~15	
Leukocytosis (>9.5×10^3/mm^3)				
No	42	14.5	9~21	0.153
Yes	64	10	9~13	
Neutrophilia (>75%)				
No	30	11	8~19	0.534
Yes	76	11.5	9~15	
Lymphopenia (<20%)				
No	16	11	8~22	0.626
Yes	90	12	9~15	
Thrombocytopenia (150×10^3/mm^3)				
No	69	14	11~17	0.186
Yes	37	9	5~11	
Hyperbilirubinemia (>1.2 mg/dL)				
No	71	13	10~19	0.008
Yes	34	9	5~13	
Hypoalbuminemia (<3.5 g/dL)				
No	27	18	8~26	0.218
Yes	78	10.5	9~14	
Azotemia (>1.2 mg/dL)				
No	92	11	9~15	0.307
Yes	13	10	4~NA	
CRP level*, 6.58 mg/dL				
Low	53	15	11~20	0.212
High	52	9	6~13	
Ferritin level*, 796.5 ng/mL				
Low	42	13.5	11~21	0.006
High	41	9	8~14	
Indication for CDS				
Delirium/agitation	42	12	7~19	0.314
Dyspnea	19	10	6~24	
Pain	44	11	9~17	
Drug used for CDS				
Lorazepam	12	21.5	15~NA	0.048
No lorazepam	94	10.5	9~13	
Haloperidol	48	14.5	9~20	0.165
No haloperidol	58	10	8~13	
No. of drugs for CDS				
1	55	10	8~13	0.035
2	41	14	9~17	
3 & 4	10	21.5	11~NA	

CDS: continuous deep sedation, GI: gastrointestinal, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, PPI: Palliative Prognostic Index, CRP: C reactive protein, MST: median survival time, CI: confidence interval.
*Based on the median value in the current sample. †Using the log-rank test of the Kaplan-Meier method.

DISCUSSION

In this study, the survival time began not at the initiation of CDS but rather at the start of in-patient hospice care. The

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Table 2. Survival Analysis Using the Cox Proportional Hazard Model.

Variables	Age-and sex-adjusted		Backward multivariate*	
	HR (95% CI)	P	HR (95% CI)	P
ECOG-PS=4	1.59 (1.03~2.46)	0.038	1.78 (1.02~3.08)	0.041
PPI>6	1.68 (1.10~2.56)	0.016	2.18 (1.29~3.66)	0.003
Leukocytosis	1.37 (0.92~2.05)	0.126		
Neutrophilia	0.92 (0.59~1.44)	0.725		
Lymphopenia	0.91 (0.53~1.56)	0.721		
Thrombocytopenia	1.33 (0.88~2.01)	0.176		
Hyperbilirubinemia	1.90 (1.23~2.93)	0.004	2.04 (1.16~3.58)	0.013
Hypoalbuminemia	1.33 (0.85~2.08)	0.205		
Azotemia	1.37 (0.76~2.46)	0.299		
High CRP	1.26 (0.85~1.87)	0.243		
High ferritin	1.97 (1.23~3.15)	0.005	2.28 (1.36~3.80)	0.002
Dyspnea (vs. delirium)	1.02 (0.59~1.76)	0.958		
Pain (vs. delirium)	0.82 (0.53~1.27)	0.379		
Haloperidol use	0.74 (0.50~1.10)	0.136		
Lorazepam use	0.55 (0.30~1.02)	0.057		
No. of CDS drugs	0.74 (0.55~0.98)	0.037	0.60 (0.43~0.86)	0.005

ECOG PS: Eastern Cooperative Oncology Group Performance Status, PPI: Palliative Prognostic Index, CRP: C reactive protein, HR: hazard ratio, CI: confidence interval, CDS: continuous deep sedation.
*Including selected variables (P<0.05) in the univariate analysis.

reason for this was that it was difficult to determine the exact time of CDS initiation through retrospective medical records and that the survival time after the initiation of CDS is typically only 1 day based on the results of prior studies [11,15]. When determining the exact time of CDS initiation is difficult, the analysis can instead use information from the time of hospitalization or registration [16] and take subsequent caution when interpreting the results. Therefore, the results of this study reflect characteristics from the beginning of hospitalization related to the survival time of patients who had refractory symptoms that necessitated CDS.

In principle, palliative sedation requires progressive sedation. Of course, there continues to be controversy about the speed of sedation progression [17]. In this study, the progression from palliative sedation to CDS was not clear; however, it must be understood that the patients had refractory symptoms that necessitated CDS. The prognostic factors identified in this study (low function, high PPI scores, hyperbilirubinemia, high blood ferritin levels, and others) have already been previously identified as prognostic factors in terminal cancer patients. For patients with highly severe symptoms, the significance of those factors was considered to have been maintained. Administering a higher number of sedatives indicated that it took more time to reach CDS, thus also increasing the patient's recorded survival time.

The sedatives used for palliative sedation have their strengths and limitations [18]. Midazolam is fast-acting, but the range of responses varies by patient, and while the patient response to lorazepam tends to have less variation than midazolam, more time is needed to reach maximum effectiveness when administering lorazepam. Diazepam, which was the primary drug used in this study, reaches its maximum effectiveness quickly, but when it is injected over a long period of time, the sedative effect from its metabolites is cumulative. This limitation, however, can make it a stable and effective sedative in the context of a hospice ward where the need is mainly for irreversible sedation.

This study has the following limitations. First, since the study retrospectively reviewed medical records, data on the continuous evaluation of symptoms and important information including changes in consciousness after sedation that could have affected the results were not obtained. Moreover, since there was no control group composed of individuals who did not receive CDS, the study could not examine the effect of

CDS itself on survival. Second, since the study was based on experiences within a single institution, the generalizability of the findings is limited. It is possible that different trends would be observed in primary and secondary hospice hospitals or at other types of hospice facilities. Third, various factors that can influence sedation, including the socioeconomic background of patients and family members, were not included in the analysis. Despite these limitations, this study provides valuable data about CDS in the context of in-patient hospice care. As public interest in end-of-life care increases following the implementation of South Korea's Act on Decisions on Life-Sustaining Treatment, it is expected that end-of-life guidelines suited to a South Korean context will be developed based on the results of various studies.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR'S CONTRIBUTIONS

Conception or design of the work: ICH. Data collection: HKA, ICH. Data analysis and interpretation: all authors. Drafting the article: HKA. Critical revision of the article: HYA, ICH. Final approval of the version to be published: all authors.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.14475/jhpc.2021.24.4.254.

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Supplementary Table 1. Patient Characteristics (N=106).

Characteristics	Total (%)	Mean ± SD
Age (yr)		65.2 ± 12.8
Sex		
Female	35 (33.0)	
Primary cancer site		
Hepato-Biliary-Pancreatic	29 (27.4)	
Gastrointestinal (esophagus, stomach, colorectal)	24 (22.6)	
Lung	20 (18.9)	
Genitourinary (bladder, prostate, cervix, ovary, endometrial)	13 (12.3)	
Breast	11 (10.4)	
Other	9 (8.5)	
Drugs for CDS		Maintenance dose
Diazepam	105 (99.1)	33.8 ± 20.6
Haloperidol	48 (45.3)	6.0 ± 2.1
Lorazepam	12 (11.3)	8.3 ± 5.0
Midazolam	2 (1.9)	
Indication for CDS		
Pain	44 (41.5)	
Delirium/agitation	42 (39.6)	
Dyspnea	19 (17.9)	
Others	1 (0.9)	

Data are presented as number (%) or mean ± SD.
SD: standard deviation, CDS: continuous deep sedation.

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