Original Article

Clinical Patterns of Continuous and Intermittent Palliative Sedation in Patients With Terminal Cancer: A Descriptive, Observational Study

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Abstract

Context. Limited information is available regarding the detailed clinical patterns of palliative sedation (PS), that is, the symptom control rate, salvage medication, and the effectiveness of intermittent PS (IPS) versus continuous PS (CPS).

Objectives. The primary aim was to investigate clinical outcomes of PS in a real clinical setting.

Methods. Clinical information was prospectively collected for patients who were treated according to a prescribed protocol and assessment tools in a hospice unit affiliated with a tertiary cancer center between September 2015 and March 2017. Data were analyzed retrospectively. Midazolam was used as the first medication for PS, and propofol and phenobarbital were subsequently used as salvage medications. Indications of PS, the depth of sedation, the quality of sleep, and the level of consciousness were assessed.

Results. A total of 306 patients were enrolled, 89 of whom (29.1%) received PS. No difference in survival time was found between patients with and without PS (median survival, 34.0 vs 25.0 days, $P = 0.109$). Delirium was the most common indication of PS. The symptoms of 73 (82.0%) of 89 patients with PS were relieved with midazolam. Twelve (75.0%) of 16 midazolam-failure patients responded to propofol, five of whom (31%) exhibited respiratory depression. Of the 89 patients receiving PS, 61 (68.5%) received IPS and 28 patients (31.5%) received CPS. The median survival times from PS initiation to death were six days in the IPS group and one day in the CPS group ($P < 0.001$). Interestingly, consciousness levels were significantly improved after IPS in the delirium group compared with those in the other group (41.7% vs 16.7%, $P = 0.002$).

Conclusion. The refractory symptoms of end-of-life patients with cancer can ultimately be relieved with various medications for PS. IPS may improve the consciousness level of patients with delirium. J Pain Symptom Manage 2019;58:65–71.

Key Words

Sedatives, intermittent palliative sedation, continuous palliative sedation, survival

Introduction

Patients with advanced cancer suffer from various symptoms. Some patients suffer from intractable symptoms despite active measures by professional medical teams. Palliative sedation (PS) is a last resort for mitigating these refractory symptoms at the end of life, reflecting an ethically established use of PS.[1,2] The medical justification and effectiveness of

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PS have been demonstrated, and guidelines have been developed to ensure appropriate applications of PS in clinical practice.[1,3] Most physicians involved in hospice care agree with the implementation of PS for patients with refractory symptoms or for whom death is imminent.[4] However, despite the consensus on the usefulness of PS, many issues related to its clinical application have not been addressed, including the timing, medications, and sedation type.[1,5–7] The appropriate time for implementing PS varies from hours to weeks of life expectancy depending on the guidelines referenced.[8–10] Many guidelines suggest midazolam as a first-line medication, although some guidelines do not recommend any medication because of a lack of solid evidence.[3,11] Although more than 80% of patients with an indication for PS can experience relief with midazolam,[12] some patients do not respond to midazolam and require salvage medications. Barbiturates, including phenobarbital or propofol, are suggested as second- or third-line agents.[13] Surprisingly, few studies have investigated the clinical outcomes of salvage sedation.

PS is classified into continuous and intermittent sedation by sedation type. Continuous palliative sedation (CPS) involves intentionally inducing unconsciousness in a patient until death and is clearly distinct from euthanasia. A study revealed that CPS does not shorten the survival of patients and is not sufficiently dangerous to strictly enforce the principle of double effect.[14] However, caregivers and even medical professionals are often confused about the conceptual distinction from euthanasia because patients pass away without awakening after receiving sedatives.[15] Compared with CPS, intermittent palliative sedation (IPS), which is also called respite or temporary sedation, involves administering sedation for a limited time, discontinuing the drug, and awakening the patient. A study suggested that IPS can be safely used for several months and allows consciousness reversibility.[16]

However, few studies have reported how PS is performed and the subsequent results and comparisons of these two types of sedation are especially lacking. The primary aim of this study was to identify the clinical patterns of PS according to a prescribed protocol and assessment tools.

Patients and Methods

Study Design

We performed an observational study with all consecutive patients who were hospitalized at a single hospice center affiliated with a tertiary medical center in Korea between September 2015 and March 2017. The hospice ward had 13 beds, and two palliative care specialists with more than 10 years of experience in terminal cancer were responsible for inpatient care. Nurses were also familiar with PS through standardized protocols and education. The protocol was determined by the palliative care team based on the literature and previous experience. PS has been carried out under the protocol since August 2015. The specific protocol is described below. Information was prospectively collected regarding clinic-pathological variables, indications for PS, adverse events, the depth of sedation, the quality of sleep, and the level of consciousness. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of the medical center (IRB No: GNUH 2016-01-004-004).

The Protocol for Palliative Sedation and Assessment Tools

PS was performed in accordance with a predetermined protocol when patients met the following four conditions:

1. Severe uncontrollable symptoms despite optimal treatment strategies.
2. Patients and/or family members were aware of the condition and its irreversibility.
3. Consent was provided by patients and/or family members.
4. Patients and/or family members understood the possibility that patients may die in an unconscious state or experience sudden deterioration after PS.

Midazolam was the first choice among medications. Propofol and phenobarbital were used if midazolam failed. Medications were selected based on individual patient characteristics. Midazolam, phenobarbital, and propofol were given by intravenous bolus injection or rapid infusion at the start of PS at doses of 1–5 mg, 100–200 mg, and 0.25–0.5 mg/kg, respectively. Maintenance doses of midazolam, phenobarbital, and propofol ranging from 0.5 to 2 mg/hour, 25 to 50 mg/hour, and 0.25 to 2 mg/kg/hr, respectively were then infused.

The drugs were administered with careful titration to reach the minimum sedative dose required to achieve cessation of refractory symptoms. Vital signs including blood pressure, respiratory rate, and oxygen saturation on an oximeter were checked 15 and 30 minutes after injection and then carefully monitored periodically. The medication dosage was adjusted to relieve patients' severe symptoms while inducing a minimal decline in consciousness.

The depth of sedation was evaluated using the Richmond Agitation-Sedation Scale (RASS), which is used to standardize sedation based on the response to PS.[17] The RASS has 10 levels of agitation and sedation, where positive scores indicate the severity of agitation

Table 1
Patient Characteristics of the Study Population

	Total ($N = 306$)		Did Not Receive Palliative Sedation ($N = 217$)		Received Palliative Sedation ($N = 89$)		
	N	%	*N*	%	*N*	%	*P*-value
Sex							
Male	208	68.0	137.0	63.1	71	79.8	0.005
Female	98	32.0	80.0	36.9	18	20.2	
Age, years (mean, SD)	65.8	11.8	66.5	12.1	64.1	11.0	0.098
Primary cancer							
Lung	78	25.5	53	24.4	25	28.1	0.942
Breast	13	4.2	11	5.1	2	2.2	
Gastric	41	13.4	27	12.4	14	15.7	
Colorectal	25	8.2	17	7.8	8	9.0	
Pancreatobiliary	57	18.6	43	19.8	14	15.7	
Genitourinary	25	8.2	18	8.3	7	7.9	
Head and neck	8	2.6	5	2.3	3	3.4	
Hematologic	16	5.2	12	5.5	4	4.5	
Hepatocellular	22	7.2	15	6.9	7	7.9	
Others	21	6.9	16	7.4	5	5.6	
Discharge status							
Alive	54	17.6	41	18.9	13	14.6	0.413
Death	252	82.4	176	81.1	76	85.4	

and negative scores reflect the level of sedation. The definitions of individual scores are as follows:

+4: combative, +3: very agitated, +2: agitated, +1: restless, and 0: alert and calm; −1: drowsy, −2: light sedation, −3: moderate sedation, −4: deep sedation, and −5: unarousable.

Owing to the lack of established outcome measures for the quality of sleep available in this setting, we used an ad hoc symptom-based grading scale ranging from grade 1 to grade 5.

> Grade 1: Sleep without awakening.
> Grade 2: Sleep with awakening once or twice during sedation.
> Grade 3: Moderately successful sleep with awakening more than three times during sedation.
> Grade 4: Occasional sleep, overall wakefulness.
> Grade 5: Inability to fall asleep.

Survival was defined as the period from hospitalization to death or discharge. The sleep scale and RASS were evaluated according to the average conditions of patients by the nurses caring for them. Evaluations were performed between one and six hours after sedation initiation with either IPS or CPS, followed by another evaluation the next morning. All nurses were trained on the assessment scales to enhance inter-rater reliability.

Survival from PS initiation to death was calculated. The point at which IPS failed and was switched to CPS was set as the start time of IPS or the "zero point." Sleep quality was assessed in all sedated patients, whereas mental status changes were assessed only in patients receiving IPS.

Statistical Analysis

Descriptive statistics were summarized as frequencies and percentages for categorical variables. PS was defined as successful when the RASS score was −1 or less with no further complaints of intolerable symptoms. If patients did not experience relief of their refractory symptoms with IPS and were switched to CPS, these cases were classified as CPS. Categorical variables were compared using the chi-squared test or Fisher's exact test. Survival was estimated using the Kaplan-Meier method, with between-group comparisons performed using log-rank tests. Statistical Package for the Social Sciences software, version 16.0, for Windows (SPSS Inc., Chicago, USA) was used for the statistical analysis. A *P*-value of <0.05 was considered significant.

Results

Demographic and Clinical Characteristics

A total of 306 patients were enrolled in the prospective cohort, and their demographic and clinical characteristics are summarized in Table 1. Among them, 89 patients (29%) received PS. Patient characteristics were not significantly different between patients with and without PS, except for a male predominance for PS (63.1% vs 79.8%, $P = 0.005$). The most common primary cancer was lung cancer (25.5%), followed by pancreatobiliary (18.6%) and stomach (13.4%) cancer. Most patients (85.4%) died during hospitalization. The median survival time of all patients was 28.0 days. However, no difference in survival was noted between the groups with and without PS (median survival time, 34.0 vs 25.0 days, $P = 0.109$).

Treatment and Outcomes of Palliative Sedation

Table 2 shows the symptom control rates. Midazolam was effective after administration in 79 (88.8%)

Table 2
Efficacy of Palliative Sedation

Drugs for PS	No. of Patients	No. of Symptoms Relieved (%)	Cumulative Symptom Control Rate (%)
First-line: Midazolam	89	73 (82.0)	82.0
Second-line: Propofol	16	12 (75.0)	97.8
Refractory to midazolam	7	5 (71.4)	
Tolerant to midazolam	9	7 (77.8)	
Third-line: Phenobarbital	3	3 (100.0)	100.0

of 89 patients, whereas 10 patients (11.2%) required another medication to alleviate refractory symptoms. Sixteen patients, including nine patients who developed tolerance to midazolam, received salvage agents. Second-line propofol alleviated the symptoms of 12 (75.0%) of 16 midazolam-failure patients. Three patients received phenobarbital as a third-line medication. Among the 89 sedated patients, two patients (2.3%) were discharged alive. The most common indication for PS was delirium (54 patients, 61%), followed by dyspnea (18 patients, 20%) and pain (13 patients, 15%). The median duration of PS was 5.0 days (interquartile range [IQR]: 1.5−11.5 days), and the median survival time after initiation of PS was 5.0 days (IQR: 2.0−15.0 days). The median dose of midazolam used was 2 mg/hour (range: 1−4 mg/hour), and the median dose of propofol used was 2 mg/kg/hour (range: 1−3 mg/kg/hour).

All 89 patients eventually achieved relief of intractable symptoms with PS. Of the 89 patients, 86 patients were assessed for sedation levels. Midazolam induced moderate sedation in 62 (72%) patients (Fig. 1). The median RASS score was −3 for both midazolam and second-line propofol. Sleep quality was assessable in 62 patients. The median grade was 2 with both midazolam and propofol, indicating that patients only awoke once or twice during sedation.

No fatal events causing hastening of death were noted. A decreased respiratory rate developed in 10 (11%) patients receiving midazolam, although none of these patients exhibited a decrease in oxygen saturation. Paradoxical agitation developed in 10 patients (11%). Four patients experienced both side effects. Compared with midazolam, propofol caused respiratory depression in five of 16 patients (31%). The respiratory rate decreased to a range of 3/min to 11/min. Three patients exhibited a decrease in oxygen saturation to a level of 80%−88%. Paradoxical or persistent agitation occurred in three patients.

Comparison Between Intermittent and Continuous Palliative Sedation

Of the 89 patients in the PS cohort, 61 patients (67.8%) received IPS and 28 patients (32.2%) received CPS, including 17 patients with failed symptom control by IPS. Unlike the patients receiving IPS, the most common indication among 11 patients who initially selected CPS was dyspnea (five patients), followed by delirium (three patients) and pain (three patients). However, no statistically significant difference was found between the two cohorts ($P = 0.08$). The median survival times from the initiation of IPS and CPS were 6.0 days (IQR: 3.0−6.0 days) and 1.0 day (IQR: 0−2 days), respectively ($P < 0.001$).

Table 3 shows the effect of IPS on mental status. Thirty-seven patients had delirium before IPS, 15 of whom (40.6%) showed an improved mental status after IPS. However, other symptoms were not improved after PS. No improvement in delirium was observed in the CPS group.

Discussion

Although many previous studies have investigated PS, literature containing detailed information for clinical practice is limited. Here, our study suggests three informative issues that were difficult to find in the existing literature.

First, our study showed the clinical outcomes of salvage medication. We used a protocol designating propofol as a second-line alternative agent and phenobarbital as a third-line agent from the start of PS. Although guidelines suggest propofol as a PS agent for the management of intolerable symptoms in dying patients, no research is available on its salvage use or even first-line application except for case reports.[1,18] Our data showed the efficacy (75%) of propofol in midazolam-failure cases.

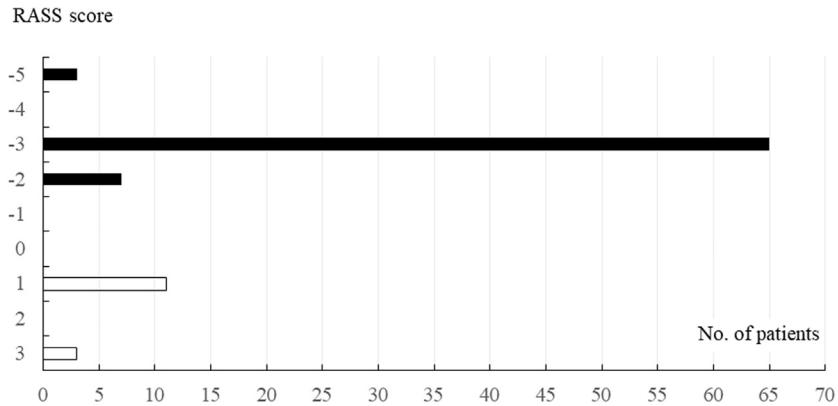

Fig. 1. Depth of sedation after midazolam PS. Black bars indicate negative score of RASS, while white bars represent positive score. PS = palliative sedation; RASS = Richmond Agitation-Sedation Scale.

Table 3
Characteristics and Comparison Between Intermittent Palliative Sedation and Continuous Palliative Sedation

Characteristics	Intermittent Palliative Sedation, $N = 61$ (%)	Continuous Palliative Sedation, $N = 28$(%)	*P*-value
Gender			1.000
Male	49 (80.3)	22 (78.6)	
Female	12 (19.7)	6 (21.4)	
Age, median (range)	64.0 (56.5 - 72.0)	68.5 (56.5 - 74.8)	0.425
Median dose (mg) of midazolam (range)	2.0 (1.0 - 3.0)	2.0 (2.0 - 3.0)	0.506
Mental status changes between the first and second days after PS			
Unchanged	20 (40.8)	8 (32)	0.047
Improved	26 (53.1)	10 (40)	
Worse	3 (6.1)	7 (28)	
Mental status changes between the first and second days after palliative sedation in subjects with delirium			
Unchanged	16 (43.2)	18 (75.0)	0.002
Improved	15 (40.6)	0 (0)	
Worse	6 (16.2)	6 (25.0)	

Propofol is highly lipophilic and works through potentiation of $GABA_A$ receptor activity. Loss of consciousness occurs in less than one minute after an induction dose of 2 mg/kg and lasts for approximately five minutes.[19] Compared with midazolam, the time to reach a sedative level was significantly shorter and psychomotor recovery was faster.[20] However, the side effect of respiratory suppression is problematic. Frank LR et al. reported that eight of 50 patients experienced respiratory depression during procedural use of propofol.[21] Another study reported the frequency of hypoxia with propofol use. Among patients randomly allocated to two experimental groups, 18% of patients in the supplemental oxygen group and 28% of patients in the compressed air group experienced hypoxia.[22] Propofol induced respiratory depression in five (31%) of 16 patients. However, another study reported a rate of only 0.39% for minor events of hypoxemia in a sample of 9654 patients receiving propofol.[23] The discrepancy in the adverse event prevalence may derive from differences in doses and patient cohorts. Further studies on the respiratory effect of propofol for PS are warranted.

Second, we not only showed cross-sectional changes in consciousness after PS with midazolam but also observed successful maintenance of PS with midazolam longitudinally. Midazolam and propofol induced moderate sedation, that is, any movement to voice, and the sedative state was maintained, with awakening only once or twice during sedation. In our study, most (82.0%) end-of-life patients suffering from intractable symptoms were treated with PS using midazolam as the first-line agent. Another study reported that adequate sedation in dying cancer patients ranged between 75% and 100%.[12,24,25] However, whether symptom control using PS was maintained is unclear because the existing literature only describes cross-sectional success rates. We used five ad hoc sleep grades because PS seems to be regarded as sleeping from the perspective of caregivers. The usefulness of our sleep scale for PS will be verified in a future study.

Finally, the novelty of our study is the clinical outcome of IPS. Although PS traditionally refers to CPS, patients may mistake CPS for euthanasia despite conceptual distinction. A study revealed that 86% of surveyed people would select IPS and 72% did not want CPS.[26] However, research on IPS remains insufficient. In this study, approximately two-thirds of the patients received IPS. The data showed that IPS could generally be applied without significant irreversibility of the consciousness level. In contrast, the mental status of 15 (41.7%) of 36 delirious patients receiving IPS improved. Insomnia and delirium often coexist, and sleep disturbance may aggravate delirium in patients with terminal cancer.[27–30] Although the causal relationship between these two symptoms remains controversial, some evidence indicates that good sleep may improve delirium.[31] We also identified a case in which insomnia and delirium were improved simultaneously by IPS.[16]

The median survival time of the IPS group was longer than that of the CPS group (6.0 days vs 1.0 day, $P < 0.001$). The survival difference is presumed to derive from the worse general conditions of the patients in the CPS group rather than a harmful effect of CPS on survival. CPS was not found to hasten death.[14,32] A prospective cohort study with 1827 patients showed that the median survival times of patients with and without CPS were 22 days and 26 days, respectively ($P = 0.91$).

The present study has several limitations. First, we could not show data for satisfaction among the caregivers or family members of patients. Second, although the data were collected prospectively,

potential biases inherent to retrospective analyses could have been better avoided. In addition, interpersonal evaluation bias may have occurred because the assessments were performed by the nurses caring for the patients. Finally, because this study reflects the experience of a single center, multicenter research is needed to determine the generalizability of the results.

In conclusion, PS is effective in controlling refractory symptoms of end-of-life patients with cancer without shortening survival time. Midazolam can be used without major side effects, whereas respiratory depression must be monitored when using propofol. IPS can be safely implemented with reversibility of the mental status for end-of-life patients with cancer.

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