



Special Article

Palliative Sedation in End-of-Life Patients in Eastern Asia: A Narrative Review

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Although palliative sedation (PS) is a common practice in the palliative care of cancer patients in Western countries, there is little related research on the practice in Korea. PS can be classified into several categories according to sedation level and continuity. PS is clearly distinct from euthanasia. While euthanasia is illegal and regarded as unethical in Korea, there is little ethical and legal controversy about PS in terms of the doctrine of double effect. Most studies have asserted that PS does not shorten the survival of terminal cancer patients. Since preference for PS heavily depends on stakeholder value, it should be preceded by shared decision-making through full communication among the patient, family members, and medical team. This is a narrative review article analyzing previous studies, especially from the three Eastern Asian countries, Korea, Japan and Taiwan, which share similar cultures compared with Western countries. Practical issues concerning PS—for example, prevalence, type and dosage of medications, salvage medication, timing of its initiation, and assessment—are described in detail.

Key words End of life, Palliative care, Sedation, Refractory symptoms

Introduction

Terminal cancer patients often experience a variety of symptoms such as delirium, difficulty breathing, pain, and vomiting during the final days of their lives. These symptoms are often not alleviated, despite restorative and palliative treatments [1]. Palliative sedation (PS) refers to the suppression of the patient's consciousness through sedative drugs to alleviate intractable suffering that is unresponsive to various medications when the patient's life expectancy is mere days or weeks [2].

Public interest in the "right to die" began to rise in 1997 as the Supreme Court in the United States decided in favor of maintaining its existing stance in the states of Washington and New York on the request to lift the ban on physician-assisted suicide [3]. A medical society on palliative care published guidelines on PS and statements. These guidelines covered the field of PS process, pharmacology, culture, and types of sedation. However, since PS implementation varies depending on the values of patients and family members, culture, and healthcare systems, introducing guidelines issued from other countries without verification could be problematic.

PS can be divided into several categories according to the clinical criteria [2]. It can be divided into superficial and deep types according to the sedation level. Superficial PS main-

tains a state in which the patient is able to partially communicate with his or her family, while deep sedation keeps the patient in a complete lack of consciousness. Depending on the continuity of sedation, sedation can also be divided into intermittent and continuous sedation. Intermittent PS involves performing sedation during a certain time, mainly at night, when patients and caregivers suffer severe psychological or physical distress. In contrast, continuous PS refers to putting the patient in continuous sleep for 24 hours. Other classification criteria include the type of drugs used and the time required to reach a sedative stage.

In Korea, PS is endorsed by the guidelines for ceasing life-sustaining treatment and for terminal care published by the Korean Society of Critical Care Medicine. In the 6th edition of the Recommendations from the National Cancer Center, PS is also recommended for patients suffering from uncontrolled severe symptoms, including pain. However, both of these guidelines only provide principles rather than specific practical issues [4,5]. The "Clinical Practice Guideline Care for Last Days of Life" issued by the Korean Society for Hospice and Palliative Care introduced more detailed information about the process of PS and the types of drugs used in the process [6]. Nevertheless, this guideline has a limitation in dealing with PS in depth. This article aims to provide detailed information focusing on the practical issue of PS. The literature was searched using PubMed with the search

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title terms “palliative sedation,” “euthanasia,” “terminal sedation,” and “deep sedation.” Following a combination of MESH terms, we also searched (“conscious sedation” OR “hypnotics and sedatives/administration and dosage”) AND “terminal care.” In addition, we added three guidelines issued by the Korean Society of Critical Care Medicine, the Korean Society for Hospice and Palliative Care and the National Cancer Center.

Ethical and Social Justification

1. The ethical aspect

In the early days when the concept of PS was introduced, the term “terminal sedation” was used to clarify its meaning and to avoid confusion with terms such as physician-assisted suicide due to conceptual similarity. However, the term “terminal sedation” has led to controversies surrounding the ambiguity of the word “terminal,” whether it applies to the state of the patient or the implementation of sedation until death [7]. Thus, “palliative sedation,” which clearly indicates the purpose of the treatment, was preferred [8].

While PS is completely different from euthanasia from a medical perspective, they become difficult to distinguish when applied to actual patients. The misunderstanding about PS and euthanasia is not limited to nonmedical individuals, such as patients and caregivers, but often includes medical personnel who care for cancer patients. These personnel often mistake the concept of PS for euthanasia. In particular, some claim that continuous PS, in which the patient is not awakened after initial sedation and remains sedated until death, should be regarded as a type of euthanasia because it ceases all meaningful interaction with other people until death [9]. This issue is also socially sensitive, leading to conflicts depending on the perspectives about PS. In 2003, the Attorney General of the Netherlands insisted that PS has the same effect as euthanasia and that the same laws should thus be applied [10].

When harmful adverse effects of treatment, even patient death, are expected, the ethical justification of PS is permissible in light of the doctrine of double effect [11]. There are four clauses in the doctrine of double effect, and the following four criteria must be met:

- The intention of treatment must be morally good.
- The treatment itself must be good, and any bad result should be an unintended side effect.
- A bad result must not be the way of achieving the good result.
- Beneficial effects should outweigh the harmful effects.

Applying this doctrine of double effect to euthanasia, euthanasia has a good purpose of relieving patient suffering.

However, the goal is achieved through bad actions, either murder or assisted suicide. Thus, it is against the doctrine. Conversely, PS adopts the good action of relieving pain by suppressing consciousness, and the death of the patient is an unintended side effect of sedative medication, therefore meeting all four conditions of the double effect.

Shortening of patient life is a key concern for medical personnel when implementing PS. However, existing studies have shown that PS does not lead to the acceleration of patient death. A large-scale study in Japan showed no significant differences in the average survival period between a group of 269 patients given continuous sedation and a group of 1,558 patients who were observed but not given sedation (27 days vs. 26 days) [12]. A recent large cohort prospective study in Japan revealed that there was no detrimental effect of continuous deep PS on survival in the last days of life of cancer patients (adjusted hazard ratio, 1.06; 95% confidence interval, 0.85 to 1.33) [13]. Another study in Western countries also reported that no significant difference existed in the average survival time between a group of 502 patients with continuous PS and a group of 1,912 patients without PS (10 days vs. 9 days) [14].

2. The psychosocial aspect

Although PS is generally viewed as a necessity by both the medical staff and the general public, there is a significant perceived gap in certain areas. A survey study in Japan showed that medical personnel believe that PS is clearly different from euthanasia or physician-assisted suicide, regardless of sedation type. However, the general public often believes that mild or intermittent sedation is different from euthanasia, while the general population regarded continuous PS as more similar to physician-assisted suicide or euthanasia [15]. Another study conducted in Korea also showed a clear preference for intermittent PS. Ninety-one percent of patients or their family members in hospice care wanted intermittent PS, whereas only 3% of patients opted for continuous sedation [16].

Family members can experience negative psychological symptoms due to PS. A survey study conducted in Japan revealed that bereaved families of 185 terminal cancer patients who had received PS experienced guilt, helplessness, and emotional exhaustion [17]. Another study conducted in Taiwan also reported the emotional distress of bereaved families [18]. The study found that more than 90% of the family members had doubt and concerns, wondering if there were not other options to relieve symptoms. They wished medical personnel would have provided detailed information prior to the PS, such as assuring them that they had tried their best to alleviate refractory symptoms and advising the family to prepare for the patients' death. In contrast, family

satisfaction was found to increase and distress was found to decrease after explicit explanation about PS. A study in Japan reported that 78% of family members expressed satisfaction with PS and that only 25% experienced emotional distress after explicit explanation of PS [19].

Generally, given the nature of PS, with patients unable to participate in decision-making due to the deterioration of their entire body systems, families make the decision regarding PS. However, when patients are aware of their prognosis and have a long duration of hospice care, they can more actively participate in this discussion. A qualitative study in Korea showed that patients and their families in the hospice ward had little basic knowledge of PS [20]. The majority of patients and their families in the study believed that decision-making on PS should be made prior to the worsening of symptoms. The Clinical Practice Guideline Care for Last Days of Life created by the Korean Society for Hospice and Palliative Care also recommends shared decision-making based on communication among patients, their caregivers, and medical personnel prior to engaging in PS [6]. Therefore, prior to conducting PS, it is essential to communicate with the patients and their caregivers regarding the irreversible nature of recovery, lack of alternatives for symptom control, and preparation for the death of the patients. A systematic review study indicated a lack of patient participation in decision making about PS due to their limitations of physical or cognitive capacity and therefore underscored the importance of discussion earlier in the disease trajectory [21].

The Practice of PS

1. Classification

As mentioned earlier, PS can be divided into several forms depending on the classification criteria [2]. According to the sedation level, PS can be classified into mild sedation, which allows for communication with caregivers, and deep sedation, in which the patient is close to unconsciousness. PS can be classified into continuous and intermittent sedation based on the sedation duration. In clinical practice, duration-based classifications are most often used; as continuous sedation is accompanied by a much lower level of consciousness, it is often called continuous deep sedation. Considering the time taken to sedate a patient, PS can also be divided into two categories: proportionate sedation, where the patient is sedated to the point where he or she feels that the pain is bearable and which is achieved by monitoring the level of consciousness and severity of symptoms, and rapid sedation, where the patient is quickly sedated to the point of unconsciousness, irrespective of the severity of the symptoms.

2. Cultural difference

Two essential components in performing PS are physician's effort for physical comfort in dying patients even by the application of PS and decision-making through a close communication between physician and patient or family members. There is no specific study on the perceptual difference toward PS among doctors or patients in Korea, Japan, and Taiwan. However, there were individual researches which investigated the cultural differences among the three countries on these two components. Physicians' awareness that the necessity of physical comfort for a good death was almost identical in the three countries, whereas difference existed in the patient autonomy and communication with patients in the dying phase. Exploring study on the physician's perception of good death, all three countries answered more than 6 points out of 7 scale (1=not important, 7=essential) [22]. As to physicians' attitudes toward autonomy, significant gap existed in the three countries. Another study showed the wide diversity in the communication with dying patients. Yamaguchi et al. [23] revealed that few Japanese (4.8%) and Korean (19.6%) patients were informed of their impending death, whereas 66.4% of Taiwanese were informed. More than ninety percent of families were informed in all three countries [23]. Further studies are needed to elucidate the cultural differences of perception in the PS.

3. Prevalence

The frequency of PS varies significantly depending on the disease, cultural differences, the care environment, and the types of sedative treatments. In a nationwide study of 23 Austrian palliative healthcare institutions, the frequency of sedation varied greatly between 0% and 54%, with a higher frequency observed in hospitalized patients [14]. Another large cohort observational study in Italy reported that 5% of patients in home care and 21% in hospice care received PS [24].

In a retrospective study of 8,309 terminal cancer patients who died in seven tertiary healthcare institutions in Korea, the proportion of PS varied from 7%-50% [25]. The same study also showed wide differences according to the institutions, the physicians' careers, and the areas of study ranging from 10% to 55%. Concerning differences in the types of palliative treatment, another study that analyzed 306 hospitalized patients in a single hospice institution in Korea showed that 29% of the patients received PS, among whom 69% received intermittent sedation and 31% received continuous deep sedation [26].

4. Timing and indication

The Clinical Practice Guideline Care for Last Days of Life recommends considering PS when patients in the terminal phase suffer from refractory symptoms [6]. However, there are some differences among institutions in defining what constitutes the terminal phase. The European Association for Palliative Care defines this period as a few hours to a few days, whereas the Royal Dutch Medical Association and National Hospice and Palliative Care Organization in the United States recommend PS to patients with life expectancy within two weeks [3]. In any case, patients and caregivers have little understanding of PS or life expectancy and want medical personnel to provide relevant explanations before the patient's conditions worsen significantly [20]. The right to self-determination is a core principle in the view of bioethics. Therefore, it is desirable to ask patients whether to implement PS at an earlier time when he or she has full cognitive function rather than to ask family members before imminent death. The most common indication for considering sedation is delirium. In the majority of the existing literature, 50% or more of the indications for PS were delirium, followed by dyspnea and pain [2]. However, unlike intractable physical symptoms, which are unanimous indications of PS, existential suffering, such as loss of life motivation and decreased social energy, is a controversial indication [27]. Regarding the legitimacy of PS for existential suffering, consensus has not been reached on whether it is suitable even after application of the double effect principle. Therefore, more caution should be taken in the implementation of PS in these cases [28].

5. Decision making progress

Since wide perceptual differences existed regarding recognition of PS in the physician and patient/family members, shared decision-making through sufficient communication among patients, their caregivers, and medical personnel is indispensable prior to PS. Morita et al. [15] reported that physicians considered continuous deep PS closer to mild and intermittent PS, while the general population regarded continuous deep PS as physician-assisted suicide/euthanasia. Since the general public can misunderstand continuous palliative sedation as euthanasia, detailed explanation and communication should be premised in advance. Three-talk model of shared decision making process, i.e., team talk, option talk, decision talk, can be applied in reaching conclusion [29]. Team talk is the stage of rapport development with process of inviting the patient and family members as a partner in the decision-making and emphasizing the goal of comfort. Option talk is to provide various information on the effectiveness and risk of PS that can be selectable to patients. Decision talk is the process to reach agreement with patients and family members whether performing PS or not by

incorporating the patient's values and preferences. When the use of the procedure is decided upon, a consent form must be signed stipulating the agreement for its use. The consent form must include the patient's name, the main subjects involved in the decision, the symptoms driving the need for PS, the purpose and expected side effects of PS, and the specific method of sedation [6].

6. Medications

Regarding sedatives, the majority of the guidelines recommend midazolam, which has a fast onset and short half-life and thus has a shorter effect duration once injection is discontinued [3]. Midazolam starts taking effect within 1 minute of administration, reaching its maximum effect between 2 to 5 minutes; its half-life ranges from 1 to 3 hours, typically lasting for 2 hours [30]. Conventionally, 2-5 mg is repeatedly administered until the patient is sedated; once the patient enters sedation, 1-5 mg per hour is administered for the desired length of time. Side effects, while rare, include paradoxical responses in patients, such as anxiety and agitation. Flumazenil is an antidote for the reversal of benzodiazepine-induced toxicity. A prospective observational study in Japan reported that using midazolam in PS led to low blood pressure and respiratory depression in 20% of the patients; 3.9% of the cases were fatal [31].

Haloperidol is a psychoactive drug that is primarily considered for controlling delirium through the mechanism of dopamine inhibition. It can be considered the optimal treatment method with sedative effects proportionate to its dose in theoretically uncontrollable delirium. However, there are limitations to using haloperidol to control refractory delirium in terminal patients [30]. The first reason is that patients in the end-of-life phase often have accompanying symptoms to delirium, including pain and dyspnea, which are not responsive to haloperidol. The other reason is the paucity of evidence that high doses of haloperidol are superior to smaller doses for refractory delirium [32]. Furthermore, given that the patient's life expectancy is within a few days, it is necessary to consider changing to different medications or a combination of therapies rather than simply increasing the haloperidol dose. Hui et al. [33] showed that a combination of haloperidol and lorazepam was more effective than haloperidol alone in terminal cancer patients with delirium.

An increased use of opioids for alleviating pain or dyspnea may be accompanied by decreased consciousness. However, increasing dosages of opioids for the purposes of PS may fail to induce the desired level of sedation or lead to side effects such as increased sensitivity to pain, convulsions, and dyspnea. Therefore, the use of opioids is not recommended for the purposes of PS [3]. When patients are nonresponsive to midazolam, many guidelines recommend phenobarbital

or propofol as secondary drugs. However, limited data are available for addressing the effect of salvage medications. We reported the clinical result of propofol as a secondary medication after failure of midazolam [24]. Sedative effects were achieved in 12 of the 16 cases (75%). However, side effects of respiratory depression were found in five cases (31%). Another small retrospective study reported the efficacy of propofol in the use of PS [34]. All 14 patients achieved sedation and adequate symptom control with respiratory adverse events in two patients. Only one study has been published on the use of phenobarbital in PS [35]. The literature describes the application of suppository phenobarbital formulations in 31 home hospice patients without sedative effects or adverse events. Therefore, although the guidelines recommend them as secondary medications after the failure of midazolam, careful use of those medications is required considering the lack of practical data. Further research is warranted to address salvage medications in PS.

Assessment of PS

The evaluation of PS efficacy is usually performed from the observer's point of view. As the primary objective is sedation to the level of symptom control, the Richmond Agitation-Sedation Scale and the Ramsay Sedation Scale are the most used to measure the effect of sedation [30,36]. In a prospective observational study of 102 patients in 21 palliative care institutions in Japan, 83% of patients using midazolam or phenobarbital achieved satisfactory sedation [31]. A retrospective study of 82 patients in Korea also reported that midazolam led to sufficient sedative effects for symptom control in 82% of the patients [26]. Relief of refractory symptoms leads to caregiver satisfaction. A focus group study investigated relatives' experiences with PS, and most respondents revealed positive feelings, including the beneficial impact of PS on the patient's suffering and involvement in decision-making [37]. From the perspectives of physicians and nurses, the study revealed that PS appropriately alleviated the symptoms and increased caregivers' satisfaction with treatment, contributing to the quality of care in the terminal periods of patients [38].

Although most guidelines emphasize the necessity of monitoring after PS, the range of recommendations is wide in terms of the details of outcome parameters and methods of assessment [39]. Some guidelines provide very specific recommendations, such as "frequent monitoring of vital signs for intermittent PS, but refraining from checking vital signs in continuous deep sedation," whereas the other guidelines mention at the fundamental level the "need to observe adverse events and effects." Some guidelines use patients'

state of consciousness and level of sedation as indicators. The Clinical Practice Guideline Care for Last Days of Life by the Korean Society for Hospice and Palliative Care also recommends careful observation every 20-40 minutes to determine whether patients' symptoms have improved, whether side effects are present, and whether the desired sedation level has been reached [6]. However, all of these indicators are evaluated by medical personnel, not by patients themselves. The use of technical approaches such as electroencephalography and electrocardiography is increasing. Validated assessment tools are insufficient to measure possible adverse events [36].

Conclusion

PS differs from euthanasia, and there is little room for ethical, social, and legal controversy around this topic. Detailed and explicit information on PS should be provided to patients and their family members before symptoms worsen and the patient's consciousness decreases, and subsequent shared decision making regarding its application should be followed. PS can be safely performed with midazolam in the majority of cases. Moreover, various topics on PS have not been sufficiently addressed, and further research is needed.

Author Contributions

Conceived and designed the analysis: Lee SH, Kwon JH, Won YW, Kang JH.

Collected the data: Lee SH, Kwon JH, Won YW, Kang JH.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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