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Brief Communication

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Current Status and Future Directions of Research on Palliative Sedation

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Patients with terminal cancer experience very severe symptoms during the end of life, and palliative sedation (PS) may be considered if those symptoms are refractory to any other treatment. This brief report presents ethical considerations, practices, and recent concerns on PS. PS is quite different from euthanasia. There is a lack of consensus and standards on protocols, but its notable effects have been reported in hospice care settings. Most studies to date have reported no difference in survival between patients receiving PS and those not, and PS must be conducted proportionally with the lightest level of sedation. The most common indication for PS is delirium, and midazolam is the main sedative used. It is recommended that information regarding PS should be provided to patients and their caregivers repeatedly as early as possible. Existential suffering alone is not an indication for PS, and there is a lack of evidence on bispectral analysis. Additional research on PS is needed in Korea.

Key Words: Deep sedation, Neoplasms, Palliative care, Terminal care

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INTRODUCTION

Patients with terminal cancer experience various severe symptoms during the end of life, and these symptoms are often refractory to any other treatment. At this time, palliative sedation (PS) is one option to consider [1]. Although PS has been widely used in clinical practice and is fairly effective, no consensus has yet been reached on its indications, the depth of sedation, appropriate methods, the choice between intermittent or continuous sedation, and its applicability to patients who have not reached the dying process due to limitations in research resulting from ethical issues. However, there is no disagreement on the fact that healthcare providers should constantly question themselves until they are convinced of refractoriness [2]. This brief report covers current issues, including ethical considerations related to PS, issues related to medical treatment being implemented, and research topics to be investigated in South Korea in the future. The reviews on PS in South Korea include the clinical guidelines [3] published by the Korean Society for Hospice and Palliative Care and the recent study by Lee [4] that reviewed previous studies conducted in East Asia.

MAIN TEXT

1. Ethical considerations

1) Impact on survival duration

Since PS theoretically suppresses cardiopulmonary function, the concern was raised that it might hasten death. A study in Japan reported that cardiopulmonary function was significantly suppressed in 20% of patients, and about 4% died

[5]. To answer the question of whether PS hastens a patient's death, a suitable starting point is a systematic review [6] published in 2012. Among the 11 studies analyzed, there were no randomized clinical trials, and inter-study heterogeneity was too high for a quantitative meta-analysis. However, the study concluded that PS did not hasten the death of patients with terminal cancer. In order to overcome the heterogeneity of previous studies, a study with the largest sample size at that time was conducted in Japan [7] and reported that there was no difference in survival duration between patients who received PS after hospitalization and controls among 1,827 patients with terminal cancer from 58 institutions across Japan. Nonetheless, that study also did not consider the exact timing of PS. A multi-center study conducted without clear guidelines pointed out a concern about differences between institutions [8]. A study conducted with consideration of these issues reported that the survival duration was instead longer in patients who received PS [9].

In summary, there is currently no evidence that PS hastens patients' death, but it is expected that the depth of sedation is closely related to the survival duration. Therefore, the lightest level of sedation that can control symptoms is recommended, and a gradual induction of sedation is strongly recommended.

2) Difference from euthanasia

Although there was a concern for some time that PS could be confused with euthanasia in countries where euthanasia is permitted, such as Belgium and the Netherlands, this point has been clarified now [10]. PS reduces the level of consciousness through the administration of sedative-hypnotics for the purpose of relieving symptoms, and the time until death is unknown. In contrast, euthanasia involves administering lethal medications for the purpose of death, and the act ends at the same time as the patient's death.

2. Clinical applications

1) Rate of performing palliative sedation

Since the protocol for PS has not been established and studies have defined PS differently, it is difficult to compare and quantitatively synthesize findings between studies. In an Austrian study, there was an institution that did not perform a single case of PS, whereas an institution performed PS in 55% of patients [11]. An Italian study reported that PS was performed in 15% of patients at home and 21% of hospitalized patients [12]. In South Korea, Kim et al. conducted a large-scale study. PS was performed within the last 2 weeks before death in 16.1% of 8,309 cancer patients who died at seven tertiary hospitals, and this rate varied substantially depending on the attending physicians' specialties-13.9% in oncology, but 54.6% in family medicine [13].

2) Decision-making process

It is recommended that information regarding PS should be provided to patients and their caregivers repeatedly as early as possible before symptoms worsen. If it is clear that symptoms are severe and refractory to treatment, the application of PS is considered according to the following considerations [2]. First, do the expected benefits, such as symptom relief, surpass the expected harms, such as decreased consciousness? Second, is the decision made based on wishes and autonomy of the patient and his or her caregivers? Third, do the members of the palliative care team understand PS and have reached substantial agreement for PS, and are the intentions pure (Figure 1)?

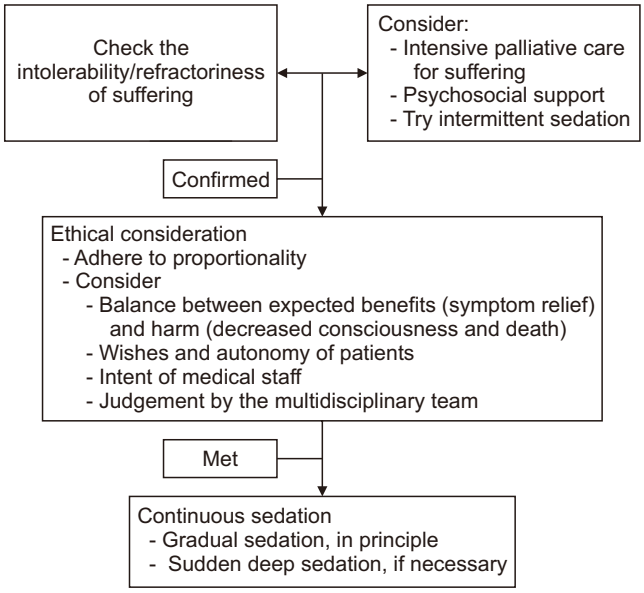

Figure 1. Flow chart for palliative sedation.
Source: Imai K, Morita T, Akechi T, Baba M, Yamaguchi T, Sumi H, et al. The Principles of Revised Clinical Guidelines about Palliative Sedation Therapy of the Japanese Society for Palliative Medicine. J Palliat Med 2020:23:1184-90.

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Table 1. Commonly Used Medications through the Intravenous Route for Palliative Sedation.

Medication	Onset	Duration	Advantages	Disadvantages
Midazolam	<5 min	1~6 h	Short half-life (=high reversibility)	Variable responses
Lorazepam	1~5 min	12~24 h	Consistent responses	Slow titration (=delayed peak effect)
Diazepam	1~3 min	≥12 h	Rapid titration	Accumulation over time with infusion
Haloperidol	Unknown	Unknown	Primarily controlling delirium	Not responsive to pain or dyspnea
Propofol	30 s	10 min	Very rapid titration	No antidote

3) Indications and medications

A recent systematic review found that the most common indication for PS was delirium, followed by pain and dyspnea, and midazolam was a commonly used medication [14]. Table 1 summarizes the commonly used sedatives, their advantages and disadvantages, and their onset time and duration when administered through the intravenous route for PS.

4) Assessment of effects and adverse reactions

The most important criterion is a patient's comfort, and symptom relief was observed in more than 80% of patients who received PS in Korean and Japanese studies [5,15]. However, a consensus on the most appropriate assessment has not been made yet in many areas, including the frequency of monitoring [16]. The tools for assessing PS vary depending on its speed. In gradual PS, clinicians observe the degree of a patient's symptom relief and simultaneously assess a patient's symptoms and depth of consciousness, whereas in sudden sedation, only the depth of consciousness is assessed [17]. The commonly used tools to measure a patient's consciousness are Ramsay Sedation Assessment Scale and Richmond Agitation Sedation Scale. According to recent studies, these scales reflect patients' symptoms and intentions well [14,18].

3. Current issues

1) Existential suffering

Existential suffering is a psychological condition with a very diverse spectrum that includes feelings of the worthlessness of life, despair, regret, remorse, fear of death, and being a burden to others [19]. Controversies persist regarding the performance of PS for existential suffering. In a study conducted in the Netherlands, where euthanasia is permitted, more than one-fourth of patients who received continuous PS reported existential suffering [20], but fewer than 1% of patients reported existential suffering in Japanese studies [21].

Most guidelines do not recommend performing PS only for existential suffering, since existential suffering does not mean imminent death and refractoriness is hard to ensure due to the possibility of improvement [10].

2) Bispectral analysis

Debate continues regarding whether sedation actually makes a patient not feel suffering, or whether a patient feels suffering but simply cannot respond. It was also reported that about 60% of patients who received general anesthesia had some subjective experiences under anesthesia [21]. Bispectral analysis can suggest an answer to these questions. A recent systematic review [23] concluded that the correlation between bispectral analysis results and clinical indicators is low, and the clinical implications of bispectral analysis are insufficient. However, at this point, when these issues are unclear, it is recommended to keep using the medications previously used to control pain and dyspnea, even if a patient's consciousness decreases due to sedation [10].

3) Future research in Korea

Very little research on PS has been conducted in South Korea. In Japan, where public opinion and ethical standards are very similar to those of South Korea, nationwide surveys on PS [24,25] have been systematically conducted for a long time. In addition, studies have investigated the awareness of nurses working at hospice institutions [26], differences in attitudes between nurses and physicians [27], and inconsistencies in the impact of PS on bereaved families [28,29]. Therefore, additional research on PS in South Korea seems necessary.

CONCLUSION

In summary, although clinical guidelines have not been established, PS is an effective option for refractory symptoms in terminally ill patients. Discussions on PS are recommended to be conducted frequently and as early as possible. Furthermore, patients, caregivers, and the palliative care team should regularly communicate with each other until refractoriness is ensured. Finally, in order to stimulate interest in PS, discussions should be held, and research should be conducted through the formation of interest groups within academic societies.

CONFLICT OF INTEREST

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

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.14475/jhpc.2022.25.4.193.

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