Survey of Palliative Sedation at End of Life in Terminally Ill Heart Failure Patients
— A Single-Center Experience of 5-Year Follow-up —

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Background: Little is known about palliative sedation in terminally ill heart failure (HF) patients.

Methods and Results: We retrospectively reviewed terminally ill HF patients who received palliative sedation from September 2013 to August 2018. Among 95 terminally ill HF patients, 25 were prescribed dexmedetomidine and 12 were prescribed midazolam at the end of life. Richmond Agitation-Sedation Scale was significantly reduced (P<0.01), but blood pressure and heart rate were unaltered after treatment in both the dexmedetomidine and midazolam groups.

Conclusions: Prescription of dexmedetomidine and/or midazolam might be feasible in selected terminally ill HF patients.

Key Words: Heart failure; Palliative care; Sedation

Heart failure (HF) is a progressive disease with a poor prognosis and is a major growing public health problem worldwide in aging societies. Palliative care is a multidisciplinary approach to improving quality of life and is highly relevant for HF patients. Palliative sedation is considered to be a therapeutic option as part of palliative care when symptoms become uncontrollable and intractable at the end of life. To date, there are limited reports and no specific recommendations about palliative sedation in terminally ill HF patients. Thus, the aims of this study were to survey the practice of palliative sedation in patients with HF at a tertiary cardiovascular referral center in Japan, and to investigate the feasibility of sedative agents in terminally ill HF patients.

Methods
Study Design and Population
This was a single-center retrospective study conducted by members of the Palliative Care Team at the National Cerebral and Cardiovascular Center, which is a tertiary cardiovascular referral center in Japan. Palliative Care Team activities commenced in September 2013 and we retrospectively reviewed consecutive patients who were hospitalized and referred to the Palliative Care Team between September 2013 and August 2018. Based on a review of Palliative Care Team consultations, patients who were hospitalized for HF and died during the hospitalization despite optimal pharmacological and/or nonpharmacological therapy were selected and defined as terminally ill HF patients. We excluded patients who were intubated or receiving mechanical circulatory support at the time of death. Patients who were administered intravenous sedation within the last week at life were defined as patients receiving palliative sedation and were included in this analysis. Among patients without palliative sedation, we investigated the reasons of non-usage and the patients’ baseline characteristics. Palliative sedation was preceded by thorough discussion with the multidisciplinary Palliative Care Team and attending doctors, and was administered to the patients with intractable severe symptoms that were refractory to ordinary palliative care approaches at the end of life.

Definition and Measurements
We investigated the efficacy of palliative sedation using the Richmond Agitation-Sedation Scale (RASS). Additionally, we obtained data on temporal changes in vital signs, including respiratory rate, oxygen saturation, blood pressure and heart rate, from the patients’ charts. These data were evaluated before treatment, approximately 1h after starting seda-
tive agents\textsuperscript{7,8} (in cases of patients without data approximately 1 h after treatment, we permitted data from within 24 h after treatment), and at maximum dose of sedative agents. Furthermore, we obtained detailed data on sedation, including the infusion method, rate and duration. If patients were prescribed more than 1 sedative agent, we obtained the data about the agent that was used as the first agent for sedation. In addition, 2 independent investigators (Y.H. and A.H.) investigated the main indication to sedation according to previous studies.\textsuperscript{4,9,10} We also obtained data on the patients’ background, laboratory and echocardiographic data, and concomitant drug use.

This study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center (M30-162), and conducted according to the Declaration of Helsinki.

Statistical Analysis
Continuous variables are presented as mean±standard deviation when normally distributed and as median and interquartile range when non-normally distributed. Comparison of baseline characteristics between the 2 groups was made using unpaired Student’s t-test or Mann-Whitney U test for continuous variables and chi-squared test or Fisher’s exact test for dichotomous variables, when appropriate. Paired t-test was applied to test the difference between variables before and after treatment. All tests were two-tailed, and a value of P<0.05 was considered statistically significant. All analyses were performed with JMP version 10 (SAS Institute, Cary, NC, USA).

Results
Survey of Palliative Sedation in Terminally Ill HF Patients
During the study period between September 2013 and August 2018, a total of 301 patients were referred to the Palliative Care Team and 108 terminally ill HF patients died during hospitalization. We excluded 13 patients with intubation and/or mechanical circulatory support at the time of death. Among 95 terminally ill HF patients, 38 (40%) were prescribed intravenous sedative agents at the end of life. Among 57 patients without intravenous sedative agents, the reasons for non-usage were: depressed level of consciousness, 16; no intractable severe symptom, 18; rapid deterioration of the patient’s condition (e.g., lethal arrhythmia), 12; wishes of patient and/or family members, 6; instability of the patient’s condition, 3 (2 with hypotension and 1 with hypoxemia); and unknown, 2. Patients without palliative sedation had a lower prevalence of ischemic etiology (6 [11%] vs. 13 [34%]; P<0.01), lower plasma B-type natriuretic peptide level (863 [401, 1,259] vs. 1,202 [637, 2,628]; P=0.04), higher estimated glomerular filtration rate (25.8 [16.1, 40.4] vs. 17.8 [8.2, 30.7]; P=0.03) and lower rates of administration of inotropes (32 [56%] vs. 31 [82%]; P=0.01) and opioids (16 [28%] vs. 25 [68%]; P<0.01). Otherwise, the baseline characteristics were comparable between the 2 groups. Among 38 patients with palliative sedation, the first agent for sedation was dexmedetomidine (DEX), midazolam (MDZ) and flunitrazepam (Figure).

Baseline Characteristics of HF Patients Who Received Palliative Sedation
We investigated the clinical background, indications to sedation, sedation details, and efficacy and feasibility of DEX (n=25) and/or MDZ (n=12) in 37 of the patients (1 patient was administered flunitrazepam). The demographic and clinical characteristics of patients are presented in Table 1. Mean age was 70±15 years. Many patients were concurrently prescribed inotropes and opioids. Median B-type natriuretic peptide and creatinine levels were quite high in this population. Baseline characteristics were comparable between the DEX and MDZ groups.

Details of Sedation
Main indications to sedation were as: dyspnea, 7; general malaise, 19; delirium, 4; psychological distress, 3; pain, 3; and other, 1. All symptoms were considered refractory to ordinary palliative care treatment. Mean initial DEX dose was 0.17±0.08 µg/mL/h and maximum dose was 0.51±0.34 µg/mL/h. Mean initial MDZ dose was 0.29±0.19 µg/mL/min and maximum dose was 0.84±0.64 µg/mL/min. Duration of drug use was comparable between the 2 groups. As palliative sedation
unchanged in the DEX group.

The results of sedation scale and vital signs at baseline and maximum dose are shown in Table 3. Respiratory rate significantly decreased in the MDZ group (P<0.01), but blood pressure, heart rate, and oxygen saturation did not significantly change at maximum dose of sedative agents in either group.

Median (interquartile range) time from starting sedation to death was 7 (3, 14) days in the DEX group and 6 (2, 12) days in the MDZ group (P=0.47). Among the 37 patients, 6 (16%) died within 24 h after being started on sedative agents (4 in DEX group vs. 2 in MDZ group; P=1.00). Patients’ characteristics and vital signs at baseline were not different between those who died within 24 h of starting sedation and those who did not. However, oxygen saturation after starting treatment tended to be low (92±11 vs. 96±4%; sedation, intermittent administration of sedative agents was less frequently performed (Table 1).

Feasibility of Sedative Agents in Selected Terminally Ill HF Patients
In the entire cohort (n=37), there was a significant change in RASS (1 [0, 1] vs. −1 [−3, −1]; P<0.01) and respiratory rate (21.2±4.8 vs. 19.3±4.8; P=0.02), but no significant changes in blood pressure, heart rate and oxygen saturation approximately 1h after starting treatment. The results of sedation scale and vital signs before and approximately 1h after treatment in the DEX group and MDZ group are shown in Table 2. RASS was significantly reduced after treatment in both groups (both P<0.01). In the MDZ group, significant decreases were observed in respiratory rate (P<0.01) and oxygen saturation (P=0.02), but these parameters were unchanged in the DEX group.

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Palliative Sedation in Terminally Ill HF Patients

Palliative sedation is defined as the use of sedative medication to relieve suffering by lowering the patient’s level of consciousness or intentional maintenance of a lowered level of consciousness resulting from symptomatic treatment.11 Palliative sedation is often required for terminally ill patients to achieve acceptable symptom relief and is reported to be generally effective with limited adverse effects in patients with advanced cancer.12 In patients with HF as well, symptoms such as dyspnea, pain, delirium and general malaise may become uncontrollable at the end of life despite optimal palliative care. However, palliative sedation in terminally ill HF patients has not been established because of lack of evidence and concerns about circulatory and respiratory instability. In this retrospective survey, we found that 40% of terminally ill HF patients were prescribed intravenous sedative agents. There were various reasons that they were not used in the remaining 60% of patients. As far as we could gather from a retrospective review, there were 3 patients for whom the attending doctors decided not to prescribe palliative sedation because of unstable condition (2 patients had hypotension with systolic blood pressure <70mmHg and 1 patient had hypoxemia with oxygen saturation <85% despite maximum oxygen administration).

In this survey, we observed that sedative agents could achieve measurable sedation without serious adverse effects such as hypotension, bradycardia and hypoxemia in selected HF patients. Nevertheless, palliative sedation should be prescribed based on advantages and disadvantages identified through comprehensive discussion by attending doctors and the multidisciplinary team. Moreover, some patients died within 24h of starting sedation. Although these patients’ characteristics were not significantly different, their oxygen saturation tended to decrease after treatment. These results suggested the further importance of multidisciplinary team discussion about the indication, dosing and timing of palliative sedation, monitoring of vital signs, and sufficient consent of patients and their family members.

**Sedative Agents in HF Patients at End of Life**

When providing palliative sedation, we sometimes have difficulty in selecting the sedative agents from among MDZ, DEX and other agents. The Japanese HF guidelines recommend MDZ, a short-acting parenteral benzodiazepine, as the first choice agent for palliative sedation, although there is a lack of evidence for this recommendation. MDZ is the most frequently used drug for palliative sedation in cancer patients. It can achieve deep sedation, but may cause respiratory and/or circulatory depression. On the other hand, DEX, an α-2 agonist with analgesic and sedative properties, does not cause respiratory depression. It was reported as safe to use in children with HF in an intensive care unit. Recently, a Japanese nationwide survey of palliative care for HF reported that DEX was most commonly used for palliative sedation in real-world clinical practice. However, there have been limited studies about sedative agents in HF patients at the end of life. Our study found that the effect on the respiratory system differed among the seda-
tive agents. In the MDZ group, the respiratory rate significantly decreased after starting the drug, which might reflect the sedative effect, although there is a possibility of direct respiratory depression by this drug. We could not precisely address the reason for the respiratory system change in this retrospective study, and could not conclude which drug was suitable for palliative sedation in HF patients. At present, we have to bear in mind the possibility of respiratory depression when we use palliative sedation for terminally ill HF patients.

Regarding blood pressure and heart rate, both MDZ and DEX did not alter vital signs after their administration and at maximum dose, suggesting the feasibility of these agents in selected terminally ill HF patients. At this time, we should select sedative agents according to the patient’s condition and the goals of palliative sedation on a case-by-case basis. Hereafter, a multicenter large-scale retrospective study and a prospective study with a fixed infusion protocol and validated measurement methods are strongly warranted.

Study Limitations
First, this was a single-center study with a relatively small sample size, so it was subject to various biases inherent in such data. Moreover, the data were analyzed retrospectively. Therefore, the timing of obtaining the clinical parameters significantly varied in each case. Patients were recruited from one national center, so generalizability is limited. Second, the RASS was not recorded in some patients and the investigators judged the sedation scale based on the description in the medical records. The interval before vital sign measurement and the drug infusion protocol were dependent on the attending physicians and nurses. Furthermore, it is difficult to measure quantitative symptom scales in terminally ill patients, and symptom scale measures were not available in this study. Third, prescription of palliative sedation was finally based on the attending doctors’ decisions. In fact, there were some differences in the baseline characteristics of patients with and without palliative sedation, resulting in unavoidable selection bias. Therefore, further studies are needed to address the feasibility of palliative sedation for terminally ill HF patients.

Conclusions
Although the effect on the respiratory system differed among the sedative agents, this single-center retrospective study suggested that palliative sedation using DEX and/or MDZ might be feasible in selected HF patients at the end of life. Nevertheless, palliative sedation should be used cautiously in terminally ill HF patients and must be discussed by a multidisciplinary team.

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Disclosures
The Authors declare no conflicts of interest.

References