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ORIGINAL RESEARCH

Effect of Dexmedetomidine for Palliative Sedation for Refractory Dyspnoea in Patients with Terminal-Stage Cancer

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Background: Dyspnoea affects a considerable percentage of patients with terminal-stage cancer, and clinical guidelines recommend palliative sedation for patients with refractory dyspnoea. Midazolam is currently the most commonly used sedative; however, it can cause serious adverse reactions, such as respiratory/circulatory depression. Hence, there is a need for an alternative sedative. Dexmedetomidine (DEX) is a promising alternative as its "awake sedation" effect; however, little is known regarding its use in patients with end-stage dyspnoea. Therefore, the aim of this study was to determine the safety and usefulness of DEX for palliative sedation of patients with refractory dyspnoea.

Methods: This retrospective study included patients with terminal-stage cancer who received DEX for palliative sedation owing to refractory dyspnoea in the hospice ward from January 2018 to October 2022. We analysed their general data, dyspnoea conditions, sedation details, sedative treatment effect, dyspnoea relief, and changes in vital signs before and after sedation, via paired *t*-tests.

Results: We included 17 patients with terminal-stage cancer who received DEX palliative sedation at a dose of 0.2–0.9 μg/kg·h for refractory dyspnoea, among whom 6 (35%) received a loading dose of 1 μg/kg in 10 min. After 1 h of sedation and at the maximum sedation dose, the Respiratory Distress Observation Scale and Richmond Agitation-Sedation Scale scores decreased significantly compared with those before sedation (all $P<0.001$), as did the respiratory rate ($P=0.024$ and $P=0.008$, respectively). The heart rate and blood oxygen saturation did not significantly change, whereas the systolic and diastolic blood pressure after 1 h of sedation were significantly lower than those before sedation (both $P=0.015$).

Conclusion: DEX is a promising palliative sedative for patients with terminal-stage cancer, as it safely relieved the symptoms of refractory dyspnoea without inducing serious adverse reactions. Therefore, DEX may greatly enhance the quality of life for patients with terminal-stage cancer.

Keywords: palliative sedation, dexmedetomidine, dyspnoea, palliative care, terminal-stage cancer

Introduction

Dyspnoea is defined by The American Thoracic Society as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity".[1] Dyspnoea is one of the most common and serious symptoms in patients with terminal-stage cancer, commonly referred to as "end-stage dyspnoea".[2] Approximately 50–70% of patients with advanced malignancies suffer from dyspnoea,[3,4] and both its prevalence and intensity typically rise as death draws near.[5–7] Dyspnoea has a substantial negative impact on patients' quality of life and can exacerbate their pain, fear, and anxiety. Current guidelines recommend that, after a comprehensive and systematic assessment of patients with dyspnoea, the reversible causes should be promptly addressed, and nonpharmacological or pharmacological interventions should be performed in patients with irreversible dyspnoea; furthermore, palliative sedation should be recommended for refractory dyspnoea that cannot be alleviated by the aforementioned treatments.[8–12]

The most frequently used sedative medicine is midazolam (MDZ); it may, however, lead to adverse reactions such as respiratory/circulatory depression after sedation, particularly in patients with end-stage dyspnoea.[13] Dexmedetomidine

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(DEX), which has sedative, anti-anxiety, and analgesic properties and does not pose a risk of severe respiratory/circulator depression, is a promising alternative for palliative sedation of patients with end-stage dyspnoea. However, studies and clinical experiences on such a use of DEX are lacking. Therefore, the aim of this study was to determine the safety and usefulness of DEX for palliative sedation of patients with refractory dyspnoea in patients, focusing on patients with terminal-stage cancer.

Methods

Patients

This study was approved by the Ethics Committee of Shengjing Hospital of China Medical University (2022PS738K) and patient privacy will be fully protected. A retrospective study was conducted on patients admitted to the Hospice Ward of Shengjing Hospital of China Medical University from January 2018 to October 2022. The inclusion criteria were as follows: (1) at least 18 years old; (2) The oncologist and the hospice physician jointly determined that the patient was in the terminal stage of the malignant tumour and died during hospitalization; (3) the presence of symptoms of refractory dyspnoea (all available interventions were ineffective, including nonpharmacological interventions, such as oxygen therapy, fan therapy, postural guidance, breathing techniques, acupressure, and reflexology, and/or pharmacological interventions, such as opioids, short-acting benzodiazepines, and glucocorticoids); (4) intravenous or subcutaneous DEX was used for palliative sedation; and (5) no invasive cardiopulmonary resuscitation procedures, such as tracheal intubation, cardiac compression, or ventilator-assisted ventilation, were performed. Patients for whom detailed records of vital signs, palliative sedation, and other data were unavailable were excluded.

Procedure

Two hospice physicians systematically collected basic information concerning patients (including age and sex), disease characteristics (including tumour type, metastasis, and tumour treatment), rating scales scores (including Karnofsky Performance Status [KPS], Palliative Performance Scale [PPS], dyspnoea visual analogue scale [VAS], Respiratory Distress Observation Scale [RDOS], and Richmond Agitation-Sedation Scale [RASS]), laboratory tests (including leukocytes, haemoglobin, platelets, albumin, total bilirubin, creatine kinase MB isoenzyme, creatinine, prothrombin time, d-dimer, fasting blood glucose, potassium, sodium, and chloride), as well as vital signs (including blood pressure, heart rate, respiratory rate, and oxygen saturation) from medical records before sedation, after 1 h of sedation, and at the maximum sedation dose. The dyspnoea VAS records the patient's subjective experience of dyspnoea intensity, whereas the RDOS records the patient's objective level of dyspnoea based on observation by medical staff. During sedation, as patients could not accurately use the VAS, only the RDOS was used. The quality and depth of palliative sedation were evaluated with the RASS.

Detailed sedation procedure: Patients received continuous intravenous or subcutaneous DEX sedation with the initial dose of 0.2–0.3 μg/kg·h and titrating to 0.2–1 μg/kg·h to achieve the desired level of sedation. The dose of DEX should be adjusted at any time during sedation according to level of sedation. A loading dose of 1 μg/kg should be administered 10 min before sedation if the patients required rapid sedation urgently (RASS score ≥ +2), and their blood pressure maintained between 140–90/90-60 mmHg with blood oxygen saturation at least 90%, otherwise no loading dose should be administered.

Statistical Analysis

The experimental data were statistically analysed using IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, NY, USA). Measurement data were expressed as the mean ± standard deviation when they were normally distributed; otherwise, they were expressed as the median (25th percentile, 75th percentile). The percentage and number of cases were used to express count data. The differences between the variables before and after palliative sedation were analysed using the paired *t*-test; and $P<0.05$ was considered statistically significant.

Results

Investigation of Dyspnoea in Patients with Terminal-Stage Cancer

A total of 1585 patients with terminal-stage cancer were admitted to the Hospice Ward for palliative treatment from January 2018 to October 2022; 943 (59.5%) of them experienced dyspnoea. Reversible causes of dyspnoea included pleural effusion, pneumonia, anaemia, and heart failure. Dyspnoea directly caused by the tumours were treated with oxygen therapy, fan therapy, and other nonpharmacological interventions, as well as opioids, short-acting benzodiazepines, glucocorticoids, and other pharmacological interventions. Dyspnoea symptoms were significantly reduced with treatment in the majority of patients with terminal-stage cancer. In this study, 17 patients who underwent palliative sedation with intravenous or subcutaneous DEX at the end of life were included, after excluding 6 patients for whom information regarding dyspnoea assessment scales, palliative sedation, or vital signs were unavailable.

General Data Analysis

The 17 patients in this study (10 men and 7 women) had an average age of 68±12 y, a median age of 70 y, a maximum age of 84 y, and a minimum age of 44 y. Among them, 12 patients had lung cancer and one case each of breast cancer, pancreatic cancer, gastric cancer, kidney cancer and cervical cancer (all with secondary lung metastasis). All 17 patients underwent anti-tumour therapy such as surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy. In combination with refractory dyspnoea, all 17 patients experienced anxiety, 14 (82%) experienced pain, and 5 (29%) experienced delirium. The dyspnoea VAS and RDOS scores revealed that anti-dyspnoea measures were ineffective, while the KPS and PPS scores suggested that the patients had terminal-stage cancer with a poor functional status and short estimated survival times (Table 1). Additionally, the laboratory test results revealed that the majority of patients had leukocytosis, anaemia, hypoproteinaemia, and abnormal coagulatory function (Table 2).

Table 1 General Data of Patients

Characteristics	Number of Cases (n=17)
Age (ys)	68±12
Sex, n (%)	
Male	10(58.8)
Female	7(41.2)
Body weight (kg)	54.1±8.2
Primary tumor, n (%)	
Lung	12(70.6)
Breast	1(5.9)
Pancreas	1(5.9)
Stomach	1(5.9)
Kidney	1(5.9)
Cervix	1(5.9)
Lymph node metastasis, n (%)	17(100)
Distant metastasis, n (%)	15(88.2)
Comorbidities, n (%)	
None	4(23.5)
One	8(47.1)
Two or more	5(29.4)
Previous treatment, n (%)	
Surgery	13(76.5)
Chemotherapy	14(82.4)
Radiotherapy	10(58.8)
Targeted therapy	9(52.9)
Immunotherapy	7(41.2)

(*Continued*)

Table 1 (Continued).

Characteristics	Number of Cases (n=17)
Accompanying symptoms, n (%)	
Pain	14(82.4)
Anxiety	17(100)
Delirium	5(29.4)
Assessment scales	
KPS (points)	24±9
PPS(%)	15±6
Dyspnea VAS (points)	9.1±0.6
RDOS (points)	14±2

Abbreviations: KPS, Karnofsky Performance Status; PPS, Palliative Performance Scale; VAS, visual analogue scale; RDOS, Respiratory Distress Observation Scale.

Table 2 Laboratory Test Results of Patients

Parameter	Value (n=17)	Reference Value
WBC (×10^9/L)	13.2±5.3	3.5–9.5
HGB (g/L)	103±28	Female:110–150; male:130–172
PLT (×10^9/L)	205±115	135–350
ALB (g/L)	30.1±3.5	35–53
TBIL (umol/L)	16.2(8.2, 20.1)	3.4–20.5
CK-MB (U/L)	29.8(17.5, 40.3)	0–24
CREA (umol/L)	61.4(42.4, 78)	Female:45–84; male:59–104
FPG (mmol/L)	7.67±3.18	3.9–6.11
K+ (mmol/L)	4.07±0.63	3.5–5.5
Na+ (mmol/L)	134.1±5.2	136–145
Cl- (mmol/L)	96.4±9.1	96–108
PT (S)	13.9±2.1	9.4–12.5
FIB (g/L)	3.53±1.78	2–4
DD (ug/L)	2016(520, 5472)	0–252

Abbreviations: WBC, white blood cell; HGB, hemoglobin; PLT, platelet; ALB, albumin; TBIL, total bilirubin; CK-MB, creatine kinase isoenzyme; CREA, creatinine; FPG, fasting plasma glucose; K+, serum potassium; Na+, serum sodium; Cl-, serum chloride; PT, prothrombin time; FIB, fibrinogen content; DD, D-Dimer.

Analysis of Palliative Sedation

All 17 patients were treated for dyspnoea, including via nonpharmacological interventions, such as oxygen therapy, fan therapy, postural guidance, breathing techniques, acupressure, and reflexology, and/or via pharmacological interventions, such as opioids, short-acting benzodiazepines, and glucocorticoids. However, the symptoms of dyspnoea were not effectively controlled in these patients. All 17 patients received palliative sedation with DEX at a dose of 0.2–0.9 μg/kg·h; the initial dose was 0.27±0.04 μg/kg·h, the maximum dose was 0.67±0.17 μg/kg·h, and 6 patients (35%) received a loading dose of 1 μg/kg in 10 min. The mean duration from initiation of palliative sedation to death was 5±5 days, the median duration was 3 (2, 5) days [the median (P25, P75)], the minimum was 1 day, and the maximum was 19 days (Table 3).

Changes in Vital Signs Before and After Sedation

After 1 h of sedation and at the maximum sedation dose, the RDOS and RASS scores significantly decreased compared with those before sedation (all $P<0.001$), as did the respiratory rate ($P=0.024$ and $P=0.008$, respectively). The heart rate and blood oxygen saturation did not significantly change after 1 h of sedation or at the maximum sedation dose, whereas the systolic and diastolic blood pressure after 1 h of sedation were significantly lower than those before sedation (both $P=0.015$), these findings were not observed at the maximum sedation dose (Table 4).

Table 3 Conditions Related to Palliative Sedation

Details of Palliative Sedation	Number of Cases (n=17)
Anti-dyspnea interventions before sedation, n (%)	
Nonpharmacologic	
Oxygen therapy	17(100)
Fan therapy	11(64.7)
Breathing postures	17(100)
Breathing techniques	17(100)
Physical therapy	6(35.3)
Acupressure and reflexology	7(41.2)
Music Therapy	9(52.9)
Pharmacologic	
Opioids	15(88.2)
Short-acting Benzodiazepines	5(29.4)
Glucocorticoids	17(100)
Bronchodilators	7(41.2)
Details of palliative sedation	
Loading dose, n (%)	6(35.3)
Duration of sedation (days)	
Mean (SD)	5±5
Median (Min, Max)	3(1, 19)
Initial dose (μg/kg·h)	0.27±0.04
Maximum dose (μg/kg·h)	0.67±0.17

Table 4 Changes of Vital Signs Before and After Sedation

	Before Sedation	1h After Sedation	*P* value	Maximum Sedation Dose	*P* value
RDOS (points)	14±2	10±2	<0.001	7±3	<0.001
RASS	2(2,3)	0(−1,0)	<0.001	−1(−2,0)	<0.001
Vital signs					
Systolic BP (mmHg)	129±21	119±22	0.015	124±25	0.124
Diastolic BP (mmHg)	79±15	72±14	0.015	74±14	0.129
Heart rate (bpm)	108±17	105±18	0.273	104±20	0.121
Respiratory rate (bpm)	29±3	27±4	0.024	25±5	0.008
Oxygen saturation (%)	94±4	93±4	0.205	94±3	0.599

Abbreviations: RDOS, Respiratory Distress Observation Scale; RASS, Richmond Agitation-Sedation Scale; BP, blood pressure; bpm, beat per minute.

Discussion

Dyspnoea is one of the most common and severe symptoms in patients with terminal-stage cancer. This condition can aggravate patients' fear, anxiety, and depression, lead to functional impairment and a decreased quality of life, affect survival, and place psychological strain on patients' families and medical staff.[14,15] Recent guidelines on dyspnoea advise that patients with end-stage dyspnoea be referred to professional palliative care teams and recommend a thorough systematic assessment that includes the intensity of dyspnoea, underlying aetiology, triggers, accompanying symptoms, psychological status, dysfunction, and quality of life. The guidelines also recommend that potentially treatable causes of dyspnoea, such as massive pleural effusion, pulmonary infection, pulmonary embolism, anaemia, and exacerbation of chronic obstructive pulmonary disease or congestive heart failure be addressed, and that irreversible and incurable tumour-related dyspnoea be treated via a combination of nonpharmacological and pharmacological interventions. When

all other treatment options have failed to relieve a patient's refractory dyspnoea, palliative sedation is recommended as a last resort.[8–12]

The practice patterns and characteristics of palliative sedation for patients with refractory dyspnoea were assessed in this single-centre, retrospective study. A total of 17 patients definitively diagnosed with malignant tumours were included. Among them, 12 patients had primary lung cancer and 5 had lung metastasis, and all received aggressive anti-dyspnoea treatment via nonpharmacological or pharmacological interventions after admission, with unfavourable results. Following a thorough systematic assessment, the patients were deemed to have terminal-stage cancer with incurable refractory dyspnoea, which were indications of palliative sedation. DEX palliative sedation reduced the patient's refractory dyspnoea, as well as the patients' and their family's anxiety and depression, allowing the patient a peaceful and comfortable end of life. During DEX palliative sedation, patients were mostly under mild sedation; hence, they could be woken up by medical personnel and family members, communicated their levels of comfort and pain, and maintain close contact with their loved ones, as needed. The initial dose of DEX was 0.2–0.3 μg/kg·h, the maximum dose was 0.4–0.9 μg/kg·h, and 6 patients received a loading dose of 1 μg/kg at the initiation of sedation. The Food and Drug Administration recommends that a loading dose of 1 μg/kg be administered 10 min before procedural sedation, followed by a maintenance dose of 0.6 μg/kg·h, and the dose can be titrated to 0.2–1 μg/kg·h to achieve the desired level of sedation.[16] In a prior study of older patients, 60% of patients who received 0.5 or 1.0 μg/kg DEX within 10 min experienced oversedation.[17] Another study revealed that a loading dose ≥0.7 μg/kg greatly enhanced the risk of cardiovascular adverse effects, such as arterial hypertension.[18] Certain doctors refrain from using loading doses because of the potential safety concerns. In our study, 35.3% of patients received the loading dose, all of whom had an RASS score ≥ +2, blood pressure maintained between 140-90/90-60 mmHg, and blood oxygen saturation of at least 90%. Rapid sedation was urgently required for these patients, and their vital signs indicated that they would be resilient to cardiovascular adverse events.

The RDOS and RASS scores of patients after sedation was significantly lower than those before sedation, indicating that DEX may reduce dyspnoea. The respiratory rates of the 17 patients during sedation and their systolic and diastolic blood pressure after 1 h of sedation were significantly lower than those before sedation. These results indicate that DEX may reduce the consciousness level of patients by reducing their central sympathetic nervous system activity, which alleviates dyspnoea symptoms and reduce their respiratory rate; the impact on their blood pressure indicates a transient hypotensive response to DEX.

Palliative sedation is defined as the application of appropriate sedative drugs to reduce the level of consciousness to varying degrees, allowing patients to perceive less or no pain at the end of life. Currently, it is regarded as an ethical and widely accepted means of palliative care intervention.[19–22] The most widely used benzodiazepine-based sedative, MDZ, has a rapid onset, short active duration, and deep sedative effect, but it may lead to respiratory/circulatory depression.[13,23] Patients with terminal-stage cancer, particularly those with end-stage dyspnoea, have an increased risk of respiratory/circulatory depression, and in our ward, we have already observed several instances of respiratory inhibition following MDZ-based palliative sedation. The highly selective α2-adrenergic agonist DEX simulates deep natural sleep by inducing a state similar to non-rapid eye movement sleep. It has sedative, anti-anxiety, and analgesic effects and it is an alternative option for palliative sedation. DEX is already frequently used for perioperative and intensive care sedation.[24,25] DEX has recently seen increased use in the field of palliative sedation in specific populations, including older patients and children, owing to its safety.[26–28] In line with the dual goals of palliative care—to relieve distress and maintain close contact with family members when necessary—patients sedated with DEX can be roused by family members and medical staff to allow communication and reporting of their comfort level.[29,30] Although DEX does not provoke respiratory depression, clinicians should be aware that it may cause arrhythmias, including atrioventricular blocks, bradycardia, QT prolongation, arterial hypertension, and hypotension, when used for palliative sedation.[28,31,32]

Multidisciplinary consultation and repeated assessments by at least two physicians are necessary to confirm that a patient has terminal-stage cancer and has refractory symptoms that are challenging to address with conventional palliative care, which are indications for palliative sedation. In such cases, the physician should explain the patient's condition and prognosis, the method of sedative administration, and any potential side effects to the patient and/or their family. If the patient or their authorized agent provides informed consent, the physician must choose the most appropriate

sedation plan according to the patient's needs. During sedation, the patient's symptoms and signs should be monitored, sedatives should be adjusted as needed, and the patient's family should be provided with ongoing psychological and spiritual support.

For palliative sedation, the level of sedation must be considered. Whether such patients should be deeply sedated or kept responsive is currently under debate.[33] Alternative sedation strategies and goals should be developed according to the patient's distress, the wishes of the patient and their family, and local policies and guidelines.[34] A frequent question from patients and their families is whether palliative sedation shortens patients' survival. In this study, palliative sedation lasted an average of 5 days, a median of 3 days, and a range of 1–19 days, which is in agreement with the results of a systematic review that the mean or median palliative sedation duration ranges from 0.8 to 12.6 days.[35] Recent studies demonstrate that palliative sedation differs from euthanasia in that it does not shorten survival but is typically used for a brief period to relieve refractory symptoms.[35,36]

This study has several limitations. First, a large-scale, multi-centre, retrospective or prospective study on palliative sedation is urgently required because this was a single-centre, retrospective study, which limited its generalisability (the generalizability of the conclusions). Second, the timing of measurement of vital signs before and after sedation was not standardised in this study, which might have influenced the accuracy of the data. Finally, the decision to administer palliative sedation, the initial dose, and choice of drug were all determined by the patient's attending physician, which might have introduced bias because there is no standard procedure for palliative sedation.

Conclusions

DEX is a promising palliative sedative for patients with terminal-stage cancer, as it safely relieved the symptoms of refractory dyspnoea without inducing serious adverse reactions, such as respiratory depression. Therefore, DEX may greatly enhance patients' quality of life with terminal-stage cancer.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical Approval and Informed Consent

The study was approved by the Ethics Committee of Shengjing Hospital of China Medical University (2022PS738K) and retrospective study was exempted from informed consent. Identifying information will be deleted when using patient data, patient privacy will be fully protected. All methods were performed in accordance with the Declaration of Helsinki.

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Disclosure

All authors declare no potential conflicts of interest in this work.

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