

The use of midazolam and haloperidol in cancer patients at the end of life

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INTRODUCTION This study aimed to describe the patterns of sedative use among terminally ill cancer patients who were referred to a hospital-based specialist palliative care service for symptom management. It also aimed to examine whether sedative use among terminally ill cancer patients during the last two days of life had any impact on their survival.

METHODS A retrospective review of case notes was carried out for patients with a diagnosis of terminal cancer, who died in a 95-bedded oncology ward between September 2006 and September 2007. Data was collected on patient characteristics, duration of palliative care, indications and doses of sedatives used at 48 hours and 24 hours before death.

RESULTS A total of 238 patients died while receiving specialist palliative care, 132 of whom (55.5%) were female. At 48 hours and 24 hours before death, 22.6% and 24.8% of patients, respectively, were on sedatives like midazolam, haloperidol or both. The median dose of midazolam was 5 mg/day while the haloperidol dose at 48 hours and 24 hours before death was 3 mg/day and 4 mg/day, respectively. The indications for midazolam were anxiety, breathlessness and stiffness, while those for haloperidol were confusion agitation and nausea. Survival analysis showed no significant difference in survival between patients who were on sedatives and those who were not. The p-value for log-rank test was 0.78.

CONCLUSION The results showed that the doses and overall frequency of sedative use in this patient population tended to be low and that usage of sedatives had no deleterious influence on survival.

Keywords: midazolam, palliative care, sedatives, survival analysis, terminal cancer
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INTRODUCTION

Sedatives have long been accepted as an effective treatment option in combating distressing symptoms like breathlessness, delirium and anxiety at the end of life.⁽¹⁻⁵⁾ Given that these symptoms have been reported in up to 88% of patients at the end of life, it is not surprising that sedative drugs have been reportedly used with similar frequency among the terminally ill, particularly in the treatment of mental anguish and terminal agitation.^(6,7) However, despite having been proven to be effective for symptom control, the use of sedatives among the terminally ill continues to be a matter of concern for many due to their perceived life-shortening effects. Some authors have even described the use of sedatives at the end of life as 'slow euthanasia'.⁽⁸⁾

Much work has been done in the field of palliative medicine using various methodologies to examine the influence of sedative drugs on survival. No sedative has thus far shown any life-shortening effects when appropriately used.^(2,6,7,9) To our knowledge, no studies on sedative use at the end of life have been conducted in Singapore to date; hence, a retrospective study was carried out to examine the patterns of sedative drug use among our patient population at the end of life. Midazolam and haloperidol are frequently used in the palliative care setting and are the focus of our attention. However, opioids, which also possess sedative properties, are administered concurrently to some patients for management of pain associated with terminal illness.⁽¹⁰⁾

Midazolam as an oral and parenteral preparation is the major sedative drug used in the local setting due to its ease of use and availability, proven efficacy as well as the prevailing prescribing habits.⁽¹¹⁾ Midazolam has been found to be effective in the treatment of breathlessness, anxiety, myoclonus and seizures that are sometimes not amenable to standard measures.⁽¹²⁾ Haloperidol is another frequently used sedative drug, particularly in the treatment of nausea, vomiting and delirium, including terminal agitation.^(11,13-18)

The main objective of this study was to describe the patterns of sedatives use (prescribed specifically for sedation) among cancer patients who were referred to a hospital-based specialist palliative care service in Singapore for symptom management and terminal care. The study also aimed to examine whether the use of these drugs among terminally ill cancer patients had any influence on their survival.

METHODS

We reviewed the case notes of all patients who died in a 95-bedded oncology ward at a tertiary care hospital in Singapore between September 2006 and September 2007. These patients were jointly managed by the oncology and consultative palliative care teams. Patients who were referred less than 24 hours before death were not included in the study. A waiver of consent was obtained from the Institutional Review Board. A total of 238 patients were included in

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Table I. Patient characteristics and cancer types (n = 238).

Characteristic	No. (%)
Age (days)*	62; 15–96
Length of stay in oncology unit (days)*	11; 1–129
Duration of palliative care (days)*	5; 1–113
Gender	
Male	106 (44.5)
Female	132 (55.5)
Primary site	
Lung	42 (17.6)
Colon	38 (16.0)
Breast	25 (10.5)
Liver	19 (8.0)
Unknown primary	15 (6.3)
Ear, nose and throat	13 (5.5)
Stomach	12 (5.0)
Ovary	7 (2.9)
Prostate	5 (2.1)
Pancreas	5 (2.1)
Nasopharyngeal	4 (1.7)
Oesophagus	3 (1.3)
Others	50 (21.0)
Metastatic site*	
Lymph nodes	115 (48.3)
Liver	108 (45.4)
Lung	89 (37.4)
Bone	68 (29.0)
Peritoneum	60 (25.2)
Spine	48 (20.2)
Brain	30 (12.6)
Adrenal	15 (6.3)
Skin	6 (2.5)

* Values are presented as median; range.

† Some patients presented with multiple metastases.

Table II. Indications for sedative medications.

Sedative and indication	No. of patients (%)
Midazolam	
Breathlessness	14 (5.9)
Anxiety	16 (6.7)
Stiffness	2 (0.8)
Breathlessness and anxiety	6 (2.5)
Breathlessness, anxiety and stiffness	1 (0.4)
Haloperidol	
Agitation	13 (5.5)
Nausea	12 (4.2)
Agitation and nausea	2 (0.8)
Confusion	2 (0.8)

the study. Data was collected on patient characteristics, duration of palliative care and patterns of use of sedative medications, including frequency and dose at 48 hours and 24 hours before death. Data analysis was carried out using the Statistical Package for the Social Sciences version 17 (SPSS Inc, Chicago, IL, USA), which included descriptive statistics, survival analysis and regression models.

Sedative drug administration was defined as prescription of traditional sedative drugs such as benzodiazepines and haloperidol with the aim of relieving distressing symptoms that were not controlled by other measures. All benzodiazepine doses were converted to Parenteral Midazolam Equivalent

Table III. Patterns of sedative use in the last 48 hours before death.

Sedative medication	No. (%)	Dose (mg/24 hr)	
		Mean; 95% CI	Median; range
Midazolam			
48 hrs before death*	30 (12.6)	7.1; 5.3–8.8	5; 1–15
24 hrs before death†	37 (15.5)	7.7; 5.8–9.6	5; 1–24
Dose category in the last 24 hrs (mg)			
No midazolam	201 (84.8)		
1–10	28 (11.4)		
> 10	9 (3.8)		
Haloperidol			
48 hrs before death*	29 (12.1)	4.2; 2.6–5.8	3; 1–19
24 hrs before death†	26 (10.9)	4.4; 2.7–6.1	4; 1–19
Dose category in the last 24 hrs (mg)			
No haloperidol	212 (88.8)		
1–10	24 (10.4)		
> 10	2 (0.8)		

*At 48 hrs before death, five (2.1%) patients had both drugs.

†At 24 hrs before death, four (1.6%) patients had both drugs. CI: confidence interval

(PME). For the purpose of analysis, midazolam doses were grouped into categories defined by Sykes and Thorns in a previous study.⁽²⁾ Dose escalation during the last 48 hours was defined as > 50% increase in dose in 24 hours, resulting in a dose of ≥ 20 mg midazolam. Survival was defined as the time between palliative care referral and death. The Kaplan-Meier method with log-rank test was used to compare the survival of patients who were on sedative drugs and those who were not, at 48 hours and 24 hours before death. Multiple regression analysis was also carried out to control for the use of opioids, as most of the patients who were on sedative drugs were also concurrently on opioids.

RESULTS

A total of 238 cancer patients were referred for palliative care, of whom 132 (55.5%) were female. The median age of the patients was 62 (range 15–96) years and the median duration under palliative care was five (range 1–113) days. The three most common primary cancers were lung (17.6%), colon (16%) and breast (10.5%). The cancer types and frequency of metastasis are shown in Table I. The major indications for use of midazolam were breathlessness, anxiety and stiffness, while haloperidol was given for symptoms such as nausea, vomiting and agitation (Table II).

At the time of palliative care referral, 16 (6.7%) patients were receiving sedative drugs. At 48 hours and 24 hours before death, 54 (22.6%) patients and 59 (24.8%) patients, respectively, were on traditional sedatives. Table III shows the patterns of use of sedative drugs as well as the mean and median doses of midazolam and haloperidol administered during the last 48 hours before death. None of our patients had dose escalation at 48 hours before death, but at 24 hours before death, four patients had > 50% dose increase from the previous day's midazolam dose. Among patients on haloperidol, one patient had dose escalation

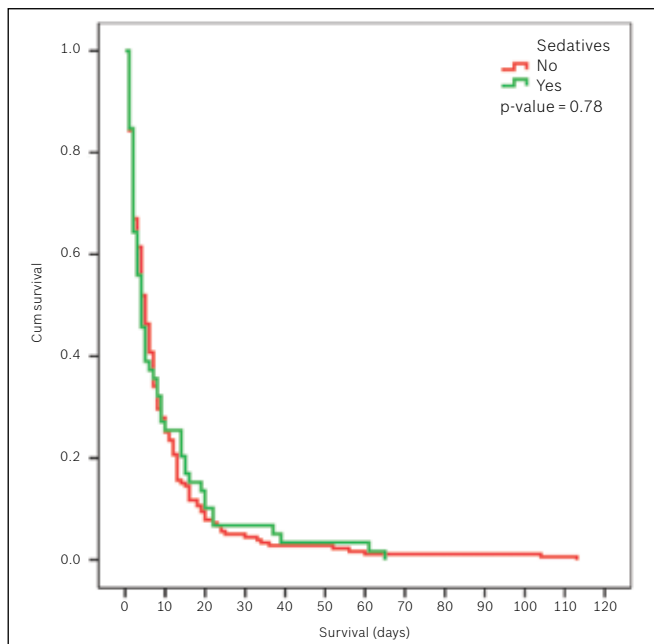


Fig. 1 Graph shows Kaplan-Meier survival curve for sedative use at 24 hours before death.

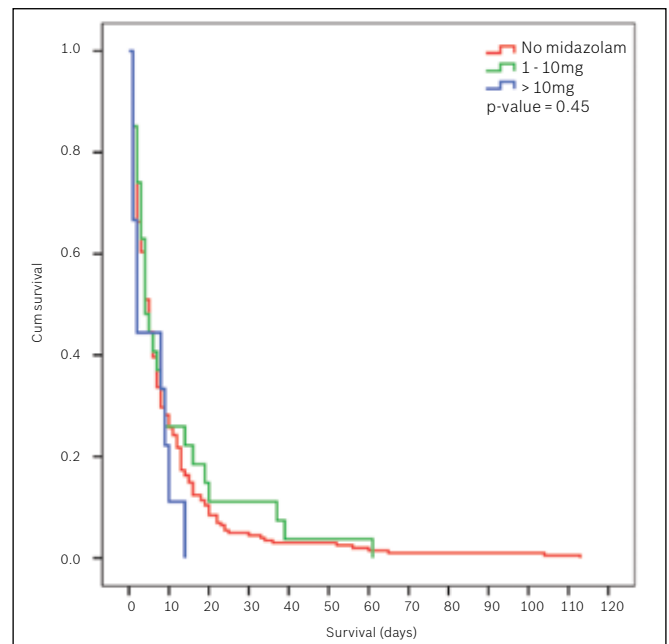


Fig. 2 Graph shows Kaplan-Meier survival curve for midazolam doses at 24 hours before death.

Table IV. Sedatives* in combination with opioids and adjuvants.

Medication	No. (%)
Sedatives only	
48 hrs before death	1 (0.4)
24 hrs before death	1 (0.4)
Opioids and sedatives	
48 hrs before death	40 (16.8)
24 hrs before death	43 (18.1)
Sedatives and adjuvants	
48 hrs before death	1 (0.4)
24 hrs before death	1 (0.4)
Opioids, sedatives and adjuvants	
48 hrs before death	12 (5.0)
24 hrs before death	14 (5.9)
Total	
48 hrs before death	54 (22.6)
24 hrs before death	59 (24.8)

*Midazolam and haloperidol

in the last 24 hours before death, reaching a maximum dose of 5 mg/day. Most of the patients who were on traditional sedatives were concurrently on opioids, and the prime indication for opioids was analgesia. Table IV shows the frequency of use of other medications like opioids and adjuvant analgesics, along with traditional sedatives.

Survival analysis using Kaplan-Meier method did not reveal any significant difference in the overall survival between patients who received parenteral midazolam and/or haloperidol and those who did not (p -value = 0.78 by log-rank test, 0.86 by Breslow). Further analysis to compare the survival patterns of patients on various dose categories of midazolam during the last 24 hours also showed no significant difference in survival. Similarly, survival curves for patients on haloperidol were compared with those who were not (Figs. 1–3). Multiple regression analysis, including additional factors such as dose and use of opioids and

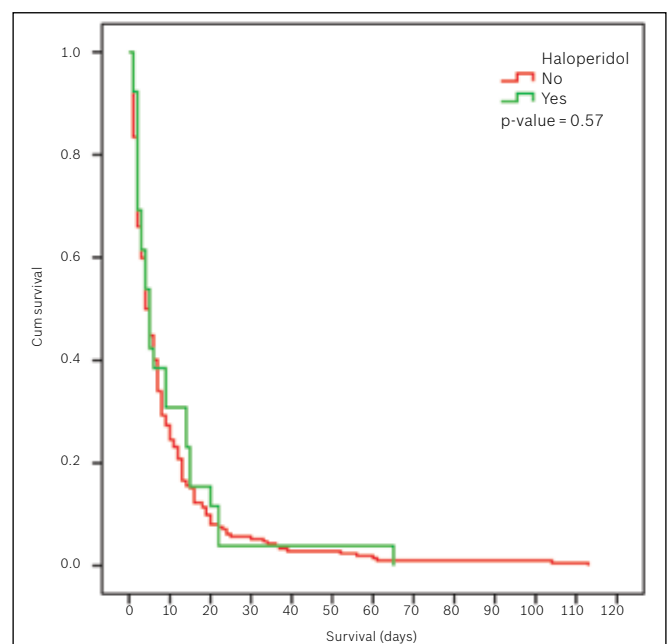


Fig. 3 Graph shows Kaplan-Meier survival curve for haloperidol use at 24 hrs before death.

adjuvants along with traditional sedatives, showed that survival was not influenced by sedative use or the dose of midazolam (Table V).

DISCUSSION

Our results show that the overall frequency of sedative use in our patient population tended to be at the lower end of the frequencies attained from other studies, which ranged from 22% to 88%.^(2,5,9,19-21) The median doses of haloperidol reported in other studies are similar to those in our study.^(5,21,22) The doses of benzodiazepines used in our setting were lower compared to those used at other centres, which reported a

Table V. Patterns of sedative use in the last 48 hours before death.

	Unstandardised Coefficients			95% CI for B	
	B	Std. Error	Sig.	Lower Bound	Upper Bound
(Constant)	7.284	1.905	0.000	3.530	11.038
Adjuvants*	3.101	1.993	0.121	-0.826	7.028
Haloperidol*	-0.812	4.982	0.871	-10.628	9.005
Traditional sedatives*	-0.009	4.995	0.999	-9.852	9.833
Midazolam dose †	-2.385	3.540	0.501	-9.360	4.591
Opioid use*	-0.559	2.177	0.798	-4.849	3.731
Opioid dose‡	7.935	1.419	0.000 ^a	5.140	10.731

Note: Patients who were on high doses had longer duration of palliative care.

* coded as 1 = yes, 0 = no

† coded as 2 = > 10 mg/24 hr, 1 = 1–10 mg/24 hr, 0 = no midazolam

‡ coded as 3 = ≥ 600 mg/24 hr, 2 = 300–599 mg/24 hr, 1 = 120–299 mg/24 hr, 0 = < 120 mg/24 hrs or no opioids

median daily midazolam dose of 30–45 mg.^(5-7,12,21,23-28) Neither the added use of haloperidol nor opioids in conjunction with benzodiazepines explained this phenomenon, and postulations as to the rationale for lower doses of midazolam in other studies did not ring true in our case.^(2,21) The relatively static doses of midazolam show that there was no development of tolerance, as reported by some authors. However, this is unsurprising given the short duration of use of these drugs.^(12,26,27,29)

An interesting consideration is whether the use of these drugs amounted to intentional sedation or amelioration of distressing symptoms at the end of life. Due to the retrospective nature of this study, we are left with merely inferences with regard to the true intention behind its implementation. As such, a review of the data regarding the incidence of loss of consciousness among patients receiving sedative drugs was carried out. Of the patients who were administered midazolam, two experienced a loss of consciousness during the last 48 hours of life. The first patient was already on midazolam when referred for palliative care. This patient was under palliative care for 19 days and had symptoms such as agitation, anxiety and breathlessness as indications for sedative use. The dose of midazolam was 8 mg at 24 hours before death for this patient. The second patient, who suffered from advanced lung cancer, experienced anxiety, breathlessness and insomnia, for which midazolam was given at a dose of 10 mg/day at 48 hours before death. Interestingly, this dose was then reduced to 5 mg/day during the final 24 hours. This patient was referred for symptom management two days before his death. During the last 24 hours before death, four patients had > 50% dose increase from the previous day's midazolam dose, of which one patient had a final dose of 24 mg/day. This patient had symptoms of breathlessness, anxiety and insomnia but did not have loss of consciousness during the last 24-hour period, and the duration of palliative care was 10 days. Thus, it could be inferred that in our patients, these sedatives were used not to induce unconsciousness but to ameliorate symptoms.

Due to ethical dilemma when considering the use of sedatives at the end of life, some physicians feel the need to use the Doctrine of Double Effect (DDE). DDE is used in medical practice as an ethical justification for a foreseeable harmful effect of a specific medical treatment when it is potentially beneficial for the patient and the clinician intends the best outcome. In our study, the use of parenteral midazolam and/or haloperidol at the end of life has not been shown to influence patient survival, which is consistent with the findings of other studies.^(2,9) This re-emphasises the fact that sedatives can be safely used for terminal symptom management without having to invoke the DDE as a matter of routine when using them at the end of life. Careful titration of these drugs with close monitoring in specific conditions would negate the need for consternation, much less the need to invoke the DDE given its relative safety.^(2,5)

There are several limitations to this study, the first and foremost being its retrospective nature. However, it would be difficult to carry out such a study prospectively without the possibility of bias and alterations in prescribing practice among clinicians. The lack of a control group reduces the strength of the findings obtained from our study. Unfortunately, conducting a randomised controlled study among this vulnerable group of patients is not an easy task given the ethical and practical issues. Generalisation is also difficult as the study was conducted on a special group of population within an oncology unit, which may not be entirely representative of all terminally ill patients. Larger studies involving various institutions in Singapore are warranted in order to build our evidence base in this area.

In conclusion, this study helps to reinforce the fact that sedative drugs can be safely used in terminally ill cancer patients. When used appropriately and titrated according to the severity of symptoms, no deleterious effects are expected. The low frequency and small doses of sedative drugs used in our patient population shows the conservative manner in which sedative drugs have been used for terminally ill patients. It is fair to assume that sedative drugs are used only with the intention of relieving distressing symptoms associated with terminal illness, as that is the routine practice in our setting. Fear of causing harm to patients is unnecessary, counterproductive and may even result in insufficient symptom alleviation. Measures such as necessary training in appropriate prescription of sedative drugs for terminally ill patients ought to be incorporated into the medical/nursing curriculum. This would empower our healthcare professionals with the knowledge required to use these drugs confidently to relieve the distress experienced by terminally ill patients without having the fear of hastening death.

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