

Opioid Use amongst Cancer Patients at the End of Life

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Abstract

Introduction: Concerns about the life shortening effect of opioids is a well known fact in the medical world when considering administration of these drugs for symptom alleviation at end of life. This study described the patterns of opioid use among cancer patients referred to a hospital-based specialist palliative care service for symptom management. This study also examined whether opioid use among terminally ill cancer patients during the last 2 days of life had any influence on survival. **Materials and Methods:** A retrospective review of case notes of patients who were diagnosed with terminal cancer and had passed away in a 95-bedded oncology ward between September 2006 and September 2007 was conducted. Data were collected on patients' characteristics and patterns of opioid use including opioid doses and dose changes at 48 hours and 24 hours before death. **Results:** There were 238 patients who received specialist palliative care, of whom 132 (55.5%) were females. At 48 hours and 24 hours before death, 184 (77.3%) patients and 187 (78.6%) patients had received opioids, respectively. The median daily doses at 48 hours and 24 hours were 48 mg and 57 mg oral morphine equivalent doses (OME), respectively. Indications for opioid use were pain (41.1%), dyspnoea, (29.1%) and both dyspnoea and pain (30.8%). In the final 24 hours, 22.3% patients had a reduction in their mean opioid dose while 22.7% required an increase in their mean opioid dose. Increased age was associated with decreasing opioid doses ($P = 0.003$). Patients with spinal metastases required higher doses of opioids ($P = 0.03$) while those with lung metastases required lower doses ($P = 0.011$). Survival analysis using Kaplan-Meier survival curve revealed no significant survival difference between those who were on opioids and those who were not. Log rank test (Mantel-Cox) ($P = 0.69$). **Conclusion:** Our results showed that opioids are safe medications for symptom alleviation in terminally ill cancer patients during the last days of life and have no deleterious influence on survival.

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Introduction

Opioid use in terminally ill cancer patients at the end of life has been a source of concern amongst many for fear of its perceived life shortening effects, despite evidence to the contrary.¹⁻¹¹ This fear has, in fact, contributed to the reluctance in utilising these drugs to provide adequate symptom relief to this group of vulnerable patients. There is a growing number of physicians who invoke the Doctrine of Double Effect (DDE) for moral reassurance when considering the administration of opioids.¹¹⁻¹⁶ 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. Patients as well as their

families sometimes perceive the administration of opioids as an augur of a poor outcome.¹³ Unsurprisingly, in actual practice, under-treatment of pain and distressing symptoms at the end of life still prevail.¹⁷⁻²¹

Given their established efficacy and bioavailability, there is no denying that opioids are the drugs of choice at the end of life, to aid in the amelioration of symptoms like pain, dyspnoea and cough.^{22,23} In fact, it has been shown that with close monitoring, safe and rapid pain control can be achieved even with significant increments in the daily opioid dose.²³⁻²⁵ Previous studies from Japan, Israel and England have examined patterns of opioid use at end of life and its influence on survival. None of them have shown that opioid use affects survival or causes hastening of death. To the

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best of our knowledge, no such studies have been conducted in Singapore before. Given the diversity of the population in Singapore, and the perceived differences in tolerability to such drugs within the Asian population when compared to the populations studied elsewhere, our study is timely and relevant.^{4,7-9,25} Only through ethically sensitive and clinically relevant research, can concerns pertaining to the use of opioids on terminally ill patients be put to rest. To this end, a retrospective study was carried out on opioid use at the end of life in cancer patients who had been referred to our hospital-based palliative care service.

Objective

The main objective of this study is to describe the patterns of opioid use among cancer patients referred to a hospital-based specialist palliative care service in Singapore for symptom management and terminal care. This study also aimed to examine whether opioid use among terminally ill cancer patients in the final 48 hours had any influence on patients' survival.

Materials and Methods

We reviewed the case notes of all patients who were diagnosed with terminal cancer and had passed away in a 95-bedded oncology ward between September 2006 and September 2007. These patients were jointly managed by the oncology and specialist palliative care teams. Patients who were seen by the palliative medical team less than 24 hours before death were not included in the study.

A waiver of consent was obtained from the Institutional Review Board to fulfill ethics requirements. Data were collected on patients' characteristics and patterns of opioid use including opioid doses and dose changes at 48 hours and 24 hours before death. All opioid doses were converted to oral morphine equivalent doses (OME) and then rounded to the nearest 0.5 and expressed in milligrams (Appendix 1).

Statistical Analysis

For the purpose of analysis, doses of opioids at 48 hours and 24 hours before death were categorised into 4 groups based on the cut-off values used in a previous study conducted by Morita et al.⁴ Additionally, we used arbitrary cut-off values of 600 mg/day or more as used by Bercovitch et al.⁸ to define very high doses of opioid in our patient population. Dose changes were also calculated for these 2 points of time before death and expressed as a fold change similar to the studies carried out by Wilcock et al.¹ and Thorns et al.⁹ Here, a 2-fold increment represents a doubling or an increase of 100% of the dose. A marked increase was defined as greater than 1.5-fold increase in

opioid dose over 24 hours at the last 48 hours and 24 hours of life.⁹

Survival time was defined as the time between palliative care referral and death. Data analysis was carried out on SPSS version 17 which included descriptive statistics, regression models and survival analysis. Multiple regression analysis was conducted to examine the factors affecting opioid doses and also to determine whether opioid doses, dose escalation or use of other drugs like traditional sedatives and adjuvant analgesics during the last 48 hours before death had any effect on survival. Finally, Kaplan Meier survival analysis with log rank test was done to examine whether there was any significant survival difference between patients on opioids and those who were not on opioids at 24 hours. Additionally, we compared survival curves of our patients according to the 4 dose categories as mentioned before.

Results

There were 238 cancer patients referred to palliative care, of whom 132 (55.5%) were females. The median age was 62 years (range, 15 to 96) and the median duration under palliative care was 5 days (range, 1 to 113). The cancer types and the frequency of metastasis are shown in Table 1. A total of 192 patients had opioids while 46 patients did not receive any opioids during their stay in the hospital. Pain was the indication for opioid use in 79 (41.1%) patients whilst dyspnoea was the indication in 54 (29.1%) patients. A combination of dyspnoea and pain was the rationale for use in 59 (30.8%) patients. Table 2 shows the patterns of opioid use at the time of referral, at 48 hours and 24 hours before death. One hundred and two (42.9%) patients were already on opioids at the time of referral to palliative care with a median dose of 30 mg/day. The median doses at 48 hours and 24 hours were 48 mg (mean = 106.3 mg) and 57 mg (mean = 100.5 mg), respectively. The frequency of patients on opioids according to the 4 dose categories termed by Morita et al.,⁴ at 48 hours and 24 hours prior to death are shown in Table 3. There were 7 (3%) patients at 48 hours prior to death and 5 (2.2%) patients at 24 hours prior to death on doses higher than 600 mg/day OME.

Table 1. Characteristics of Patients and Indications for Opioids

Characteristics	Median	Range
Age	62	15-96
Length of stay in oncology unit (days)	11	1-129
Duration of palliative care (days)	5	1-113

Table 1. Characteristics of Patients and Indications for Opioids (Contd)

Gender	Frequency, n	%
Male	106	44.5
Female	132	55.5
Total	238	100
Primary sites		
Lung	42	17.6
Colon	38	16
Breast	25	10.5
Hepato cellular	19	8
Unknown Primary	15	6.3
ENT	13	5.5
Stomach	12	5
Ovary	7	2.9
Prostate	5	2.1
Pancreas	5	2.1
Nasopharyngeal cancer	4	1.7
Oesophagus	3	1.3
Other cancers	50	21
Metastatic Sites		
Lymph nodes	115	48.3
Liver	108	45.4
Lung	89	37.4
Bone	68	29
Peritoneum	60	25.2
Spine	48	20.2
Brain	30	12.6
Adrenal	15	6.3
Skin	6	2.5
Indications for opioids		
Pain	79	41.1
Dyspnoea	54	28.1
Pain and Dyspnoea	59	30.8

*A total of 192 patients had opioids during their stay in the hospital.

Table 3. Opioid Dose, Dose Changes, Use of Adjuvants and Traditional Sedatives during the Last 2 days of Life

Opioid doses(OME) grouped (Morita Categories as mg/24hr) ⁴	At 48 hrs before death n (%)	At 24 hrs before death n (%)
No opioids	54 (22.7)	51 (21.4)
<120 mg	145 (60.9)	145 (60.9)
120-299 mg	26 (10.9)	28 (11.8)
300-599 mg	6 (2.5)	9 (3.8)
≥600	7 (2.9)	5 (2.1)
Total	238 (100)	238 (100)
Opioid dose change grouped as fold change^{1,9}		
No opioids	54 (22.7)	51 (21.4)
Decrease in opioid dose	23 (9.7)	53 (22.3)
No change	111 (46.6)	80 (33.6)
<1.5- fold increase	44 (18.5)	43 (18.1)
1.5 to 2.9-fold increase	4 (1.7)	5 (2.1)
≥3-fold increase	2 (0.8)	6 (2.5)
Adjuvants and traditional sedatives		
Steroids	30 (12.6)	29 (12.2)
Neuropathic Medications	17 (7.1)	14 (5.9)
Ketamine	2 (0.8)	1 (0.4)
Paracetamol	23 (9.7)	22 (9.2)
NSIDs	7 (2.9)	7 (2.9)
Traditional Sedatives	51 (21.4)	56 (23.5)

OME: Oral Morphine Equivalent

Table 2. Patterns of Opioid Use

Opioids(OME)	Frequency n (%)	Mean dose (mg/24hr) (95%CI)	Median dose (mg/24hr)	Range (mg/24hr)
At the time of referral	102 (42.9)	44.1(34-54)	30	1-305
At 48 hrs before death	184 (77.3)	106.3 (77.9-134.6)	48	1-1560
At 24 hrs before death	187 (78.6)	100.5 (75.4-125.6)	57	1-1440

OME: Oral Morphine Equivalent

Changes in Opioid Doses in the Last 48 hours of Life (Table 3)

At 48 hours prior to death, 23 patients (9.7%) had their opioid doses reduced whilst 111 patients (46.6%) did not receive any dose change. Fifty patients (21%) had an increase in opioid dose, of which only 2 patients had a 3-fold or more increase in opioid dose but the total doses in both these cases was less than 60 mg/day OME.

In the final 24 hours, 53 patients (22.3%) had a reduction in their opioid dose while 54 patients (22.7%) had dose increments, of which 6 patients (2.6%) had 3-fold or more increase to their opioid doses. Out of the 6 patients, 2 received 6-fold increments in their opioid requirements, arriving at final doses of 240 mg and 18 mg, respectively whilst the remaining 4 patients required final doses that ranged from 60 to 117 mg/day.

Use of Adjuvant Analgesics and Other Traditional Sedatives

Fifty-eight patients had one or more of the adjuvant medications such as steroids, neuropathic drugs like ketamine, non opioid analgesics like paracetamol or non steroidal anti-inflammatory drugs (NSAIDs) during the last 48 hours of life along with opioids for symptom control. In addition to opioids, some patients needed other types of sedatives (i.e. traditional sedatives like haloperidol, midazolam or both) for control of their symptoms such as shortness of breath, agitation, anxiety and nausea. At 48 hours before death, 51 patients (21.4%) and at 24 hours before death, 56 patients (23.5%) were given traditional sedatives along with opioids (Table 3).

Factors Affecting Opioid Dose

Multiple regression analysis was carried out to ascertain factors that may affect opioid dosing during the last days of life. Age was found to be an independent predictor of opioid dose at the end of life. Increasing age was associated with decreasing opioid doses ($P = 0.003$). Gender or primary cancer sites did not affect opioid doses. Patients with spinal metastases required higher doses of opioids ($P = 0.03$) while those with lung metastases required lower doses ($P = 0.011$) (Table 4)

Survival

Kaplan-Meier survival analysis revealed no significant survival difference between those who were on opioids and those who were not. Log rank test (Mantel-Cox) ($P = 0.69$), (Breslow test: $P = 0.692$) (Fig. 1). Interestingly, a significant finding was an increased survival in patients who received high doses of opioids as shown in Figure 2. Addition of factors like dose increment, use of adjuvants

and use of traditional sedatives as independent variables in the multiple regression model did not reveal having any significant effect on survival (Table 5).

Table 4. Factors Affecting Opioid Dose by Multiple Regression Model

Predictors	Regression Coefficients		
	B	Std Error	P
(Constant)	175.127	67.032	0.010
Age of patient	-2.125	0.713	0.003
Lung secondaries*	-51.084	19.912	0.011
Spine secondaries†	58.088	26.805	0.031
Traditional sedatives ‡	53.617	22.563	0.018
Duration of palliative care	2.765	0.712	0.000

*coded as "1" = (yes) and "0" = (no lung secondaries)

†coded as "1" = (yes) and "0" = (no spine secondaries)

‡coded as "1" = (yes) and "0" = (no traditional sedatives)

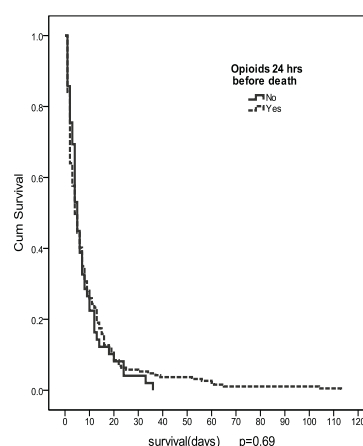


Fig. 1. Opioid use at 24 hrs before death and survival: Kaplan-Meier survival curve to compare survival.

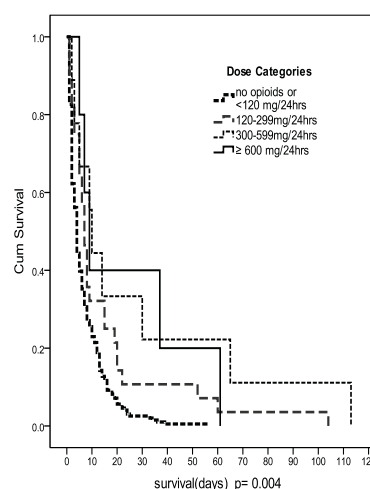


Fig. 2. Opioid doses at 24 hrs before death and survival.

Table 5. Effect of Dose Escalation, High Dose of Opioids and Use of Traditional Sedatives/Adjuvants in Survival Prediction by Multiple Regression Model

	Regression Coefficients		P	95% CI for B	
	B	Std. Error		Lower Bound	Upper Bound
(Constant)	7.290	1.896	0.000	3.554	11.027
Opioid use in the last 24hrs*	-0.413	2.178	0.850	-4.703	3.878
Traditional sedatives†	-1.895	2.064	0.359	-5.962	2.171
Adjuvants‡	3.162	1.986	0.113	-0.752	7.075
Dose escalation§	-3.502	4.097	0.394	-11.574	4.571
Opioid dose categories	7.752	1.424	0.000	4.946	10.557

*Coded as “1” = (yes) and “0” = (No opioids)

†coded as “1” = (yes) and “0” = (no traditional sedatives)

‡coded as “1” = (yes) and “0” = (no adjuvant analgesics)

§coded as “1” = (dose escalation ≥ 1.5 -fold over 24 hrs during the last 48 hrs of life) and “0” = (dose change < 1.5 fold, no dose change, decrease in dose, or no opioids)

||Coded as “3” = (≥ 600 mg/24hr), “2” = (300-599 mg/24hr), “1” = (120-299 mg/24hr) “0” = (< 120 mg/24hr or no opioids)

Discussion

Opioids have been shown to be safe when used for managing distressing symptoms at end of life in cancer patients. However, despite the presence of good evidence, physicians frequently hesitate and even withhold opioid use at the end of life for fear of hastening death. This retrospective study was carried out to provide an overview of the patterns of opioid use at the end of life and its effects on survival in cancer patients referred for specialist palliative care in a tertiary hospital in Singapore.

To put our practice into the world perspective, we compared our results with those from overseas studies. Whilst the frequency of opioid administration and median doses of opioids at the end of life were similar to those reported in other studies, the mean doses were comparatively lower among our patients. Furthermore, the number of patients found to be on high doses of opioids was also smaller than that from other studies. The frequency and magnitude of dose increments too tend to be less often and smaller than what was reported from other palliative care settings around the world, despite comparable mean ages and diagnoses.^{1,4,5,7,9,26-31} (Table 6).

Table 6. Patterns of Opioid Use: Findings from Other Studies Conducted outside Singapore

	Studies	Mean dose (mg)/day	Year	Country
Mean doses (OME) of opioids before death (mg/day)	Morita et al ⁴	136	2001	Japan
	Morita et al ²⁶	139	1998	Japan
	Bresica et al ²⁷	460	1992	USA
	Fainsinger R et al ²⁸	659	1991	Canada
	Good et al ²⁹	370.7	2005	Australia
	Studies	% of patients	Year	Country
Patients on high doses (≥ 600 mg/day) of opioids before death (%)	Portenoy RK, et al ⁵	11.7	2006	USA
	Bercovitch et al ⁷	8	1999	Israel
Patients requiring ≥ 1.5 -fold dose increments 24 hrs before death (%)	Wilcock et al ¹	52	2007	UK
	Thorns & Sykes ⁹	9	2000	UK
Patients receiving opioids before death (%)	Morita et al ⁴	87	2001	Japan
	Thorns & Sykes ⁹	89	2000	UK
	MC Cormack A et al ³⁰	85	1992	USA
	Goldberg RJ et al ³¹	66	1986	USA

OME: Oral Morphine Equivalent

The main indications for opioids in our study were pain and dyspnoea which represent the major causes of distress among cancer patients towards the end of life. This too was in keeping with other studies and further validated the utilisation of opioids in the treatment of these symptoms of dying cancer patients.^{27,28}

Similar to the studies from other parts of the world, increasing age was found to be a factor associated with lower dosages of opioids at the end of life.^{5,7,8,24,27,31-33} Unlike some studies that suggested a predilection for increase in opioid dosing with certain primary cancer sites such as cervical, prostatic, colorectal and breast cancer diagnoses, we found no such association in our sample population.^{7,27} Conversely, our results did mirror those of Bercovitch et al,⁷ when we found that patients with lung metastasis tend to use lower doses of opioids at the end of life. Furthermore, in line with other studies, we found that patients with spinal metastases tend to require higher doses of opioids than those without spinal involvement.^{7,8,27,31} Within our sample population, 3 patients required doses of opioids that exceeded 1000 mg/day. Of these, 2 patients had spinal metastasis and 1 had both spinal and bone metastases. None of them had rapid dose changes at 48 hours or 24 hours before death. Indeed, 2 of these patients were already on opioids at the time of palliative care referral and remained under palliative care for 9 days and 24 days, respectively. In the case of the third patient, the duration of palliative care involvement was 61 days. Our study, in keeping with others, revealed no significant difference in survival between those who were on opioids and those who were not, and neither was there any relationship between alterations in opioid dose and survival.^{4,5,7-9,26,29,34} Importantly and in keeping with Good et al,²⁹ our study demonstrated that patients on higher doses of opioids actually survived longer. In explaining this, we concur with Good et al²⁹ on the postulation that this group of patients may have had high symptom burden and were therefore referred early to the palliative care team. While many studies reported an increase in opioid doses at the end of life, our results showed a very small subset of patients who did.^{1,2,9,26-28,35-37} But further analysis of these patients revealed no detrimental effect on survival.

Our results show the overall use of opioids amongst cancer patients at the end of life in Singapore to be lower compared to the results of overseas studies. In part, this may reflect the relative infancy of palliative care in Singapore and the consequent scarcity of palliative care training. Other factors include a possible increased opioid sensitivity amongst the Asian population when compared to the western population. Cultural norms, religious rites and local fears associated with end of life issues also play a significant part in the decision making when dose escalations are being considered, let alone when opioids are being initiated.³⁸

Yet encouragingly, we demonstrated no significant difference in survival between patients who received opioids and those who did not. None of our patients experienced significant side effects and certainly not the frequently over-feted fear of respiratory depression. As pointed out by Fohr,³⁹ when opioids are titrated appropriately, side effects like respiratory depression is a myth and therefore such fears are misplaced.²

This study, however, has many limitations. Apart from its retrospective nature, it was not particularly designed to assess the level of symptom control achieved by opioid use. It also does not take into account the complex coadunation of factors that come into consideration as death nears. Again, the lack of a control group reduces the strength of the findings obtained from our study. Unfortunately, conducting a randomised controlled study in this patient population is not an easy task given the obvious limitations of a study among this vulnerable group in this population. Generalisation is also difficult as the study was conducted on a discrete population within a specialist unit which may not be entirely representative of all terminally ill cancer patients. Larger studies involving the various institutions in Singapore ought to be carried out to build our evidence base in this area. A closer look at the differences in opioid requirement amongst the 3 major ethnic groups would be insightful and useful. Genetic studies too can be considered amongst the major ethnic groups in Singapore to allow results to better reflect the Asian population. However, these issues notwithstanding this study clearly shows that the use of opioids in Singapore tends to err on the side of caution.

Conclusion

Reluctance among physicians in administering opioids for fear of causing deleterious effects to their patients is a well known issue in the medical world. From an ethical perspective, given the overwhelming data in support of the efficacy and safety of opioids at the end of life, failure to administer these drugs for symptomatic patients in a responsible manner is tantamount to a failure in the physician's duty of care for these dying patients. Indeed, this highlights the need to improve education to change the perception regarding the use of opioids at the end of life, both for the public and the health professional. It is hoped that this study will spur repudiation of ignorance on the safety and usefulness of opioids for symptom management towards end of life. Measures like mandatory training in appropriate analgesic prescription for alleviation of distressing symptoms experienced by terminally ill patients should be incorporated into the medical, nursing and allied health curricula. This will empower our healthcare professionals with the knowledge required to use these drugs confidently to achieve optimum symptom control

for their patients at end of life.

Old preconceptions die hard. It is hoped that these findings will help set aside some of the opioidphobia that still exists amongst our local populations fed in part by the historical associations opioids have with the fear of shortening life and addiction. In its stead, it is hoped with the help of more patient and public education will arise an acceptance that opioids at the end of life are both part of an accepted treatment at the end of life and a safe one at that.

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Appendix 1**Opioid Conversion**

Route	Types of Opioids and doses	Oral Morphine Equivalent (OME) mg
Oral	Morphine 1 mg	1
Parenteral	Morphine 1 mg	3
Transdermal	Fentanyl 12 mcg	30
Parenteral	Fentanyl 12 mcg	30
Oral	Tramadol 5 mg	1
Oral	Oxycodone 1 mg	2
Oral	Codeine 10 mg	1