Palliative Sedation in Advanced Cancer Patients: Does it Shorten Survival Time? - A Systematic Review

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ABSTRACT

Background: Patients with advanced cancer often suffer from multiple refractory symptoms in the terminal phase of their life. Palliative sedation is one of the few ways to relieve this refractory suffering.

Objectives: This systematic review investigated the effect of palliative sedation on survival time in terminally ill cancer patients.

Materials and Methods: Six electronic databases were searched for both prospective and retrospective studies which evaluated the effect of palliative sedation on survival time. Only those studies which had a comparison group that did not receive palliative sedation were selected for the review. Abstracts of all retrieved studies were screened to include the most relevant studies and only studies which met inclusion criteria were selected. References of all retrieved studies were also screened for relevant studies. Selected studies were assessed for quality and data extraction was done using the structured data extraction form.

Results: Eleven studies including four prospective and seven retrospective studies were identified. Mean survival time (MST) was measured as the time from last admission until death. A careful analysis of the results of all the 11 studies indicated that MST of sedated and non-sedated group was not statistically different in any of the studies.

Conclusion: This systematic review supports the fact that palliative sedation does not shorten survival in terminally ill cancer patients. However, this conclusion needs to be taken with consideration of the methodology, study design, and the population studied of the included studies in this review.

Key words: Intractable symptoms, Palliative sedation, Survival time,Terminally ill

INTRODUCTION

Palliative sedation is considered as one of the last resorts to relieve the refractory symptoms among dying cancer patients. The prevalence of refractory symptoms in advanced cancer is high (50-84%) with the number of individual refractory symptoms ranging from 1 to 27.[1] Although majority of the refractory symptoms can be controlled, some may remain refractory and uncontrolled till the end[2,3] and may remain unrelieved despite administering all possible treatments that are available. Palliative sedation is found to be one of the few options to relieve these intractable sufferings at the end of life.[3,4]

The first ever reported study, on palliative sedation at home settings published in 1990, found that more than 50% of patients die with uncontrolled physical symptoms that can be controlled only by means of sedation when other means of treatments fail to relieve the suffering.[5]

Notwithstanding its usefulness, several ethical questions have been raised regarding palliative sedation.[6] Is it ethical to make the patient sleep and be unaware of one's surroundings at the time of death? Is palliative sedation a modified form of euthanasia? In addition to these, there has always been a concern whether palliative sedation shortens the life span of advanced cancer patients.

Although some studies report a shortening of life span following palliative sedation,[7] others show evidence to

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the contrary.[5,8-10] The variation in results appears to be related to the sample studied, method of palliative sedation used as well as the way in which survival times have been calculated.[11]

This systematic review intends to study the available evidence regarding the effect of palliative sedation on survival time among adult terminally ill cancer patients and answers to the question: Does palliative sedation shorten survival time?

MATERIALS AND METHODS

Study design and search strategy

A systematic literature search was done in the following databases: MEDLINE, EMBASE, PsycINFO, The Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, and SCOPUS to identify papers that investigated the effect of survival time in terminally ill cancer patients receiving palliative sedation. The publications were restricted to 1980 onwards and to papers published in the English language only. The search was completed in April 2012.

Medical subject headings (MeSH) terms were identified and further exploded. The following key words were used in combinations: conscious sedation, palliative sedation, terminal sedation, continuous deep sedation, carcinoma, neoplasm, life span, survival, end of life care, palliative care, terminal care, and refractory symptoms.

In addition, a thorough hand search of the references of relevant papers was done. The authors of reputed articles on palliative sedation in different countries were contacted and requested to share their research. Letters to editor, case studies, case series, reviews, and descriptive articles were excluded

It was quite evident from earlier search that there were no randomized controlled trials (RCT) available on this topic. Therefore, it was decided to include two types of studies:

- Prospective trials with adequate control/comparative group which studied mean survival time (MST) as an outcome of palliative sedation.
- Retrospective studies with comparative group and MST as an outcome.

Another important methodological issue was, the way MST was measured in the studies. MST was measured in one of the following ways in the included studies.

- Days or hours from the start of palliative sedation to the time of death (or)
- The time between the last admission and time of death.

We decided to use the second definition time between the last admission and time of death) in this review because the first definition would not allow us to use a comparative group (comparative group is a group which was comparable to the index group but did not receive palliative sedation). The time of admission was hence taken as the beginning point.

Data extraction and study selection

Data were extracted using a specifically designated data collection form and the following were recorded: first author, year of publication, sample size, type of study (prospective and retrospective), study setting (hospice, hospital, and home care), number of patients sedated, indications for sedation, drugs used for sedation with dosage, mode of sedation (intermittent/continuous and mild/deep), mean and/or median length of sedative use (days/hours), and mean and/or median of overall survival (days/hours).

Two researchers independently screened the abstracts of all the studies that were identified by the electronic database searches and hand search. Each study was appraised using the appropriate inclusion/exclusion criteria. The inclusion criteria included:

- Adult cancer patients with one or more physical refractory symptoms,
- Palliative sedation given with any sedative, dose, or frequency,
- Presence of a comparative group, and
- MST measured in hours or days from the start of last admission until death.

Exclusion criteria included: studies in which more than 50% of study population had a non-malignant condition and where MST was not available for the non-sedated group.

Studies which met the inclusion criteria were assessed for their methodological robustness independently by both researchers according to the criteria developed by Hawker's *et al*.[12] Hawker's criteria were developed to assess the methodological rigor of disparate data.[12] As this systematic review included both prospective and retrospective studies, Hawker's criteria were found most suitable to assess the quality of the included studies.

Though the first publication of Hawker's criteria had nine items, subsequent publication included ten items, where item six was split into two (ethics and bias).[13] These criteria assess each part of the study as Good, Fair, Poor, and Very poor based on the clarity and relevance of data presented.

Each item is scored on a four-point scale (one being very poor and four being good). Maximum score possible is 40. Studies that scored below 20 were excluded. Please refer Table 1.

Statistical analysis

Descriptive data were used to measure the MST in days which was the primary outcome of this review. Because of the divergent study design and marked variability among the nature of participants, interventions, and outcomes of the included studies, it was not possible to combine the data and perform meta-analysis.

RESULTS

A total of 442 studies were identified from the search and 421 articles were excluded on the basis of title and abstract [Figure 1]. Twenty-one studies were scrutinized and of which nine studies were excluded as they did not meet the inclusion criteria. Refer Table 2 for details.

Of the remaining 12 studies, one study[9] was excluded as it had poor score when the quality appraisal tool was applied. Eleven studies were finally included in the review.

Table 1: Methodological appraisal according to Hawker's *et al.*[13]

Criteria assessed	Score (1-4)
Abstract and title	
Introduction and aims	
Method and data	
Sampling	
Data analysis	
Ethics	
Bias	
Findings	
Transferability/generalizability	
Implications and usefulness	

Table 2: Details of excluded studies

Author	Reason for exclusion
Da Costa *et al.*[14]	No comparison group
Cameron *et al.*[15]	No comparison group
Claessens *et al.*[8]	No comparison group
Peruselli *et al.*[16]	No comparison group. Not reported mean survival time
Fainsinger *et al.*[11]	No comparison group
Cowan *et al.*[17]	MST not reported separately for the comparison group
Porizio *et al.*[18]	No comparison group
Rosengarten *et al.*[19]	No comparison group
Morita *et al.*[10]	No comparison group

MST, Mean survival time

Of the 11 studies included, seven were retrospective and four were prospective studies. Four studies were conducted in hospital, four in hospice, two studies were conducted in home care, and one study in both hospital and hospice. The study characteristics are detailed in Table 3.

Total number of participants ranged from 76[20] to 548.[21] The most common indications for palliative sedation were delirium,[5,20-24,26,28,29] dyspnea,[5,20-24,26,28,29] and pain.[5,20-23,26,28,29] Six studies stated psycho-existential issues as one of the indications for sedation.[21-23,25,26,28,29]

Intermittent and continuous sedation were used in combination in six studies, whereas one study used continuous sedation alone.[28] Three studies did not state the type of sedation.[5,24,25] The level of sedation varied from mild to deep. Of the three studies that mentioned the level of sedation,[20,22,28] one study used both deep and mild sedation,[22] whereas the other study used only deep sedation.[28]

Midazolam[20,21,24,26-29] was the common sedative used and with three studies reporting exclusive use.[21,26,27] Haloperidol, levomepromazine, lorazepam, phenobarbitone, chlorpromazine, and promethazine were the other sedatives used. Two studies used morphine for sedation along with

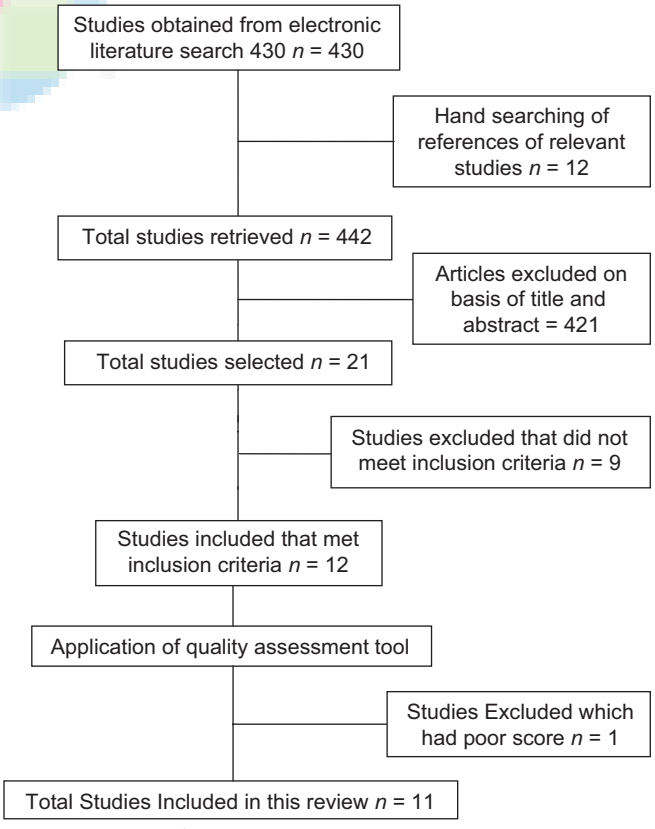

Figure 1: Search results

Table 3: Study characteristics

Author	Study settings	Study design	Total number of patients recruited	Patients receiving sedation (%)
Ventafridda *et al.*[5]	Home care	Prospective	120	63 (52.5)
Fainsinger *et al.*[20]	Hospice	Retrospective	76	23 (30.3)
Muller-Busch *et al.*[21]	Hospital	Retrospective	548	80 (14.6)
Maltoni *et al.*[22]	Hospice	Prospective	518	267 (25.1)
Chiu *et al.*[23]	Hospice and Hospital	Prospective	276	70 (27.9)
Babarro *et al.*[24]	Home care	Retrospective	245	29 (11.8)
Vitetta *et al.*[25]	Hospice	Retrospective	102	68 (66.7)
Mercadante *et al.*[26]	Hospital	Prospective	77	42 (54.5)
Sykes *et al.*[27]	Hospice	Retrospective	237	114 (48)
Reitjens *et al.*[28]	Hospital	Retrospective	157	68 (43)
Kohara *et al.*[29]	Hospital	Retrospective	124	63 (50.3)

other sedatives.[22,23] Please refer Table 4 for details of sedatives used in each study.

Primary outcome: Mean survival time

MST was calculated from the time of last admission until death. For those studies which were conducted at home care settings, MST was measured from the onset of home care until death. In this review, MST ranged from 8[28] to 63.9[24] days in the sedated group. In the non-sedated group, it ranged from 6[20] to 63.3 days.[24] In two studies,[25,26] MST was longer in the sedated group compared to the non-sedated group. Two studies[5,22] reported median survival time instead of mean survival time.

MST was of longer duration in studies conducted in home settings compared to those conducted in hospital and hospice. Two studies which were conducted at home settings reported MST of 25[5] and 63.9 days,[24] respectively. However, all the 11 studies stated that the difference between the sedated and non-sedated groups was not statistically significant. MST of all the included studies is detailed in Table 5.

Mean duration of sedation

Although this was not the primary outcome of this review, eight studies reported mean duration of sedation[20-24,26,28,29] in addition to MST. This was measured from the start of sedation until death in the sedated group. The mean duration of sedation in this review ranged between 2.5 and 4.3 days. The mean duration of sedation is described in Table 5.

DISCUSSION

The main goal of palliative care is to provide symptom relief for patients who are suffering from multiple physical symptoms.[30] When all possible medical treatments fail to relieve the intractable suffering in dying patients, palliative sedation is chosen to provide relief from suffering rather than to hasten death.[31-33]

A previous review found that the effect of palliative sedation on life span in advanced cancer patients is inconsistent between the studies.[34] However, this review had also included studies which did not have a comparative group.

Another review that explored the feasibility of palliative sedation at home settings[35] showed palliative sedation as a feasible option of treatment for patients who were dying at home. This review analyzed six studies out of which four did not have a comparative group. These two reviews looked at the mean duration of sedation rather than MST. MST in our review is not comparable with these two reviews as the definition chosen for MST is from the time of last admission until death.

MST in our review is ranging from 63.9 to 6.6 days. This wide range could be due to inclusion of studies in home care settings, wherein MST was measured from the day of enrollment until death. At home setting, patients enrolled under home care program may not be as terminally ill at the time of enrollment compared with patients in hospice or hospital settings. Their condition may be less serious and co-morbidity may be considerably less. Findings from home care settings may hence need to be considered separately. In addition to this finding, this review found that the MST in sedated group is similar or higher compared with the non-sedated groups. This is consistent with the findings of a review conducted in home care settings.[35]

Among the studies which are included in the review, those studies that do not have a comparison group reported the mean duration of sedation as survival time. This was measured from the start of sedation until death. The mean duration of sedation ranged from a low of 2.5 days[21] to a high of 4.3 days.[23] The mean duration of sedation is similar with the other reviews mentioned above.[34,35]

De Graeff *et al.*[33] in a review, that was intending to set standards on palliative sedation, do not recommend opioids as a suitable sedative for palliative sedation. It further states that even very high doses of opioids could not induce sedation in terminally ill cancer patients.[33]

Table 4: Details of sedatives used

Author	Indication for sedation	Type of sedation (%)	Sedatives used with mean dose (mg/day)
Ventafridda *et al.*[5]	Delirium, Dyspnoea Pain, nausea Vomiting	NA	NA
Fainsinger *et al.*[20]	Delirium, Dyspnoea, Pain, Nausea	Intermittent 9 Continuous 14	Midazolam 29 Lorazepam* Chlorpromazine*
Muller-Busch *et al.*[21]	Delirium, dyspnoea pain, nausea vomiting Bleeding, psycho existential	Intermittent-25.60 Continuous-38.4	Midazolam*
Maltoni *et al.*[22]	Delirium, Dyspnoea Pain, Vomiting Psycho existential	Intermittent-56.17 continuous-43.82 Propotional 8.61 Sudden-12.35 Primary-85.76 Secondary-14.23	Midazolam 41.7 Lorazepam 4.9 Chlorpromazine 55.8 Promethazine 49.3 Haloperidol 3.6, Morphine 41.2 Diazepam 25.5
Chiu *et al.*[23]	Delirium, Dyspnoea Pain, Insomnia Itching	Intermittent 52.9 Continuous 31.7	Midazolam* Haloperidol* Morphine* Chlorpromazine*
Babarra *et al.*[24]	Delirium, Dyspnoea	NA	Midazolam 73.8 Levomepromazine 125
Vitetta *et al.*[25]	Agitation, anxiety, depression	NA	Midazolam 2.2 Clonazepam 0.3 Haloperidol 0.5 Chlorpromazine* Lorazepam* Nitrazepam* Oxazepam* Phenobarbitone* Promethazine* Temazepam*, Thioridazone* Trifluperazone* Chloral hydrate* Chlormethiazole* Cyclizine* Diazepam
Mercadante *et al.*[26]	Delirium, Dyspnoea Pain, Psycho existential	intermittent-1.68 Definitive sedation 11.76	Midazolam 62.4
Sykes *et al.*[27]	Psycho existential	Intermittent-16.8	Midazolam 54.5
Reitjens *et al.*[28]	Delirium, Dyspnoea Pain, anxiety	continuous deep sedation-43	Midazolam*, Benzodiazepam* Propofol*
Kohara *et al.*[29]	Delirium, Dyspnoea Pain, nausea, Vomiting, Psycho existential	Continuous sedation-69 Intermittent sedation-30	Midazolam 51.7 to 66.7 Scopolamine* Hydrobromide*, chlorpromazine*, Flunitrazepam*, ketamine*

NA, Not available; *dose not reported

However, two studies in our systematic review used morphine as a sedative.[22,23] Maltoni *et al.*[22] stated that the mean dose of morphine used for sedation was 41.2 mg/day. However, this study did not report any adverse effect of morphine or its association with MST. Chiu *et al.*[23] mentioned the use of morphine but did not state the dose used for sedation or its association with MST. Both the studies did not mention whether morphine was effective in inducing sedation compared with other sedatives used in their study.

Table 5: The comparison of mean survival time between sedated and non-sedated group

Author	MST in sedated group in days	MST in non-sedated group in days	*P value*	Mean duration of sedation in days
Ventafridda *et al.*[5]	25 (median)	23 (median)	0.57	NA
Fainsinger *et al.*[20]	9±5	6±7	0.09	2.5
Muller-Busch *et al.*[21]	21.5	21.1	NA	2.58
Maltoni *et al.*[22]	12 (median)	9 (median)	0.330	4.0
Chiu *et al.*[23]	28.5	24.7	0.43	4.3±8.6
Alonso-Babarro *et al.*[24]	63.9	63.3	0.963	2.6
Vitetta *et al.*[25]	36. 5 (CI 20.4-52.7)	17 (CI 2.2-31.8)	0.104	NA
Mercadante *et al.*[26]	6.6	3.3	0.003	22 h (median) 2-160 h
Sykes *et al.*[27]	14.3	14.2	0.23	NA
Reitjen's *et al.*[28]	8	7	0.12	19 h (median) range 1-125 h
Kohara *et al.*[29]	28.9±25.8	39.5±43.7	0.10	3.4

MST, Mean survival time; CI, Confidence interval; NA, Not available

Palliative sedation can cause non-serious side effects such as decreased level of consciousness that results in reduced communication capacity.[32] Of the eleven included studies, three studies reported the level of consciousness. Kohara *et al.*[29] found no difference in the level of consciousness until 3 days before death between sedated and non-sedated groups. Fainsinger *et al.*[20] used an *ad hoc* scale to measure level of consciousness and found sedated patients became more drowsy and unresponsive 3 days prior to death. Mercadante *et al.*[26] found that the level of consciousness became low as the midazolam dose increased during the last days. However, this review could not find any serious side effects of palliative sedation in terminal cancer patients such as respiratory suppression without arrest, aspiration, paradoxical reaction, fatal respiratory, and circulatory suppression.

Symptom relief is the significant benefit of palliative sedation in dying patients. Three of the included studies[20,23,25] reported the level of symptom relief achieved through palliative sedation as one of the outcomes. Vitetta *et al.*[25] and Fainsinger *et al.*[20] reported good symptom control in sedated group (68% and 58%, respectively) and 34% and 40% in non-sedated groups, respectively. Chiu *et al.*[23] reported that overall 71.4% of the study population achieved symptom relief.

Although sedation is mainly indicated for intractable and refractory physical symptoms, literature supports that sedation can be given for psycho-existential issues.[32,33,36,37] De Graeff *et al.*[33] and European Association for Palliative Care[32] recommend that the decision to sedate for psycho-existential issues needs to be taken only after consulting with experts in the field. Only one study[24] in our review described how the decision to sedate for psycho-existential suffering was taken. It stated that psychologist with expertise in palliative care was consulted before the decision to start sedation.[24]

Of the eleven studies included in this review, six of them described psycho-existential reasons as one of the indications for sedation[21-23,25,26,28,29] and two studies showed a higher percentage of psycho-existential distress.[21,22] Maltoni *et al.*[22] mentioned that 6% of patients were sedated for psycho-existential suffering alone and 18% were sedated for both refractory physical and psycho-existential issues. Muller-Busch *et al.*,[21] in a retrospective study, found that 40% required sedation for psycho-existential issues and the need for sedation for psycho-existential issues had been showing an increasing trend over the 7 year study period. The author explains that this could be because of well-controlled physical symptoms due to accessible palliative care over the years in Germany, which probably led to less requirement of sedation for refractory physical symptoms and more for psycho-existential issues.

The strengths of this review include the use of different search engines, namely MEDLINE, PsycINFO, EMBASE, CINAHL, COCHRANE CENTRAL, and SCOPUS. The search was done in large database such as MEDLINE, SCOPUS, and Cochrane CENTRAL so as to cover the large number of journal articles. EMBASE which is a database for pharmacological agents was searched as this review involves sedatives. The database CINAHL was searched to find the journals published in nursing care as palliative sedation is one of the therapeutic measures of last days of dying patients.

The authors of reputed articles on palliative sedation in different countries were sent letters and were requested to share their research. All palliative care physicians in India, the editor of Indian Journal of palliative care, and the secretary of the Indian Association of Palliative care were e-mailed to share their researches, thesis, and articles waiting to be published.

The search strategy was limited to studies in the English language. Though every attempt was made to acquire studies that were not published, we might have missed dissertation, published, and other unpublished works.

The major limitation of this review is inclusion of more retrospective studies as there was a paucity of well-conducted prospective studies in this topic. Therefore, studies which investigated the MST as a secondary outcome have also been included in this review. There are no RCT that has been conducted on this area of research so far, as per our search. The prospective studies did not use blinding, so there could be bias in the outcome measurement.

Also performing quality control of selected articles was a difficult task, as there are limited tools available to assess the quality of observational studies. The quality appraisal was done using Hawker's *et al*. criteria[12] which were constructed to assess the studies with disparate data. The quality of evidence used according to this tool is poor as this has included only observational studies.

The findings of results could not be combined because of divergent study design of the included studies and the heterogeneity of data prevented us from performing a meta-analysis.

CONCLUSION

MST was not statistically different between sedated and non-sedated groups in any of the included studies in this review. However, the finding that in all studies regardless of setting, patient group, and different types of palliative sedation, the MST that did not differ from the comparison group is an important finding. However, this conclusion needs to be taken with consideration of the methodology, study design, and population studied of the included studies in this review.

Although it is ideal that the systematic review includes only methodologically sound prospective studies, in a situation where a new and a rare intervention is being studied, an initial systematic review needs to consider including retrospective studies as well. This might pave the way for design and conduct of appropriate prospective studies that will provide valid results to conduct a systematic review on this topic in future.

Pragmatic trials are recommended specially for those that deal with diverse patient groups.[38] Pragmatic trials yield results that are more useful for the clinician in situations that require different treatment options that can often not be controlled.[38,39] So conducting pragmatic trials methods might be a better solution for answering the question of survival times in palliative sedation and larger multicentric pragmatic trials may be the way forward.

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