UNIVERSITÄT AUGSBURG
Universitätsbibliothek

OPEN ACCESS
OPUS AUGSBURG

‘Palliative sedation’? A retrospective cohort study on the use and labelling of continuously administered sedatives on a palliative care unit

Eva Schildmann, Sebastian Pörnbacher, Helen Kalies, Claudia Bausewein

Angaben zur Veröffentlichung / Publication details:

Schildmann, Eva, Sebastian Pörnbacher, Helen Kalies, and Claudia Bausewein. 2018. “‘Palliative sedation’? A retrospective cohort study on the use and labelling of continuously administered sedatives on a palliative care unit.” *Palliative Medicine* 32 (7): 1189–97. https://doi.org/10.1177/0269216318764095.

Nutzungsbedingungen / Terms of use:

licgercopyright

Dieses Dokument wird unter folgenden Bedingungen zur Verfügung gestellt: / This document is made available under these conditions:
Deutsches Urheberrecht
Weitere Informationen finden Sie unter: / For more information see:
https://www.uni-augsburg.de/de/organisation/bibliothek/publizieren-zitieren-archivieren/publiz/

Check for updates

Original Article

PALLIATIVE MEDICINE

Palliative Medicine
2018, Vol. 32(7) 1189–1197
© The Author(s) 2018
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0269216318764095
journals.sagepub.com/home/pmj
SAGE

'Palliative sedation'? A retrospective cohort study on the use and labelling of continuously administered sedatives on a palliative care unit

Eva Schildmann, Sebastian Pörnbacher, Helen Kalies and Claudia Bausewein

Abstract

Background: Sedatives are frequently used towards the end of life. However, there is scarce information when their use is labelled as 'palliative sedation'.

Aim: To assess the use and labelling of 'continuous administration of sedatives within the last 7 days of life', based on objective operational criteria, on a palliative care unit.

Design: Retrospective cohort study, using medical records. Explorative statistical analysis (SPSS 23).

Setting/participants: Patients who died on a palliative care unit from August 2014 to July 2015. Sedatives recorded were benzodiazepines, levomepromazine, haloperidol ⩾5 mg/day and propofol.

Results: Of the 192 patients, 149 (78%) patients received continuous sedatives within the last week of life. The prevalence of delirium/agitation was significantly higher in patients with continuous sedatives compared to those without continuous sedatives at admission to the unit (35% vs 16%, $p = 0.02$) and on the day before death (58% vs 40%, $p = 0.04$). The term '(palliative) sedation' was used in the records for 22 of 149 (15%) patients with continuous sedatives. These patients had significantly higher total daily midazolam doses 2 days before death (median (range), 15.0 (6.0–185.0) mg vs 11.5 (1.0–70.0) mg, $p = 0.04$) and on the day of death (median (range), 19.5 (7.5–240.0) mg vs 12.5 (2.0–65.0) mg, $p = 0.01$). The dose range was large in both groups.

Conclusion: The prevalence of delirium/agitation was associated with the administration of continuous sedatives. There was no consistent pattern regarding labelling the use of continuous sedatives as '(palliative) sedation'. Multicentre mixed-methods research is needed for a better characterization of sedation practices in palliative care.

Keywords

Sedation, palliative sedation, hypnotics and sedatives, palliative care, cohort study, benzodiazepines

What is already known about the topic?

- There is no consensus regarding the definition of 'palliative sedation', that is, when the use of sedatives in palliative care is labelled as 'palliative sedation'.
- Empirical studies assess mostly self-reported 'palliative sedation', that is, labelled as such by the healthcare team and report a wide range of frequencies.

What this paper adds?

- This paper describes characteristics of patients in a German palliative care unit (PCU) who received 'continuous administration of sedatives', based on objective operational criteria.
- The terms 'palliative sedation' or 'sedation' were found to be documented only for a minority of the patients who received continuous sedatives.

Department of Palliative Medicine, University Hospital Munich, LMU Munich, Munich, Germany

Corresponding author:
Eva Schildmann, Department of Palliative Medicine, University Hospital Munich, LMU Munich, Marchioninistraße 15, 81377 München, Germany.
Email: eva.schildmann@med.uni-muenchen.de

- While patients with documentation of the term '(palliative) sedation' received significantly higher doses of midazolam 2 days before and on the day of death, there was no consistent pattern regarding the use of the label '(palliative) sedation'.

Implications for practice, theory or policy

- Multicentre qualitative and quantitative research and conceptual analysis are needed for a better understanding and characterization of sedation practices and their labelling in palliative care.
- Based on such analyses, consensus for defining different types of sedation and their differentiation from 'symptom control with secondary sedation' should be sought.
- Such consensus is needed for practitioners to know when to apply guidelines for 'palliative sedation' and for researchers to generate comparable results – two crucial factors to further promote best practice of sedation in palliative care.

Background

Some patients experience severe suffering in the last days of life from symptoms which cannot be adequately controlled by symptom-oriented treatment.[1,2] For these patients, 'palliative sedation' can be considered to relieve their suffering. 'Palliative sedation' has been defined as 'the monitored use of medications intended to induce a state of decreased or absent awareness (unconsciousness) in order to relieve the burden of otherwise intractable suffering in a manner that is ethically acceptable to the patient, family and health-care providers'.[3] Sedation is a common practice in palliative care,[4–11] with increased frequency documented for some countries in recent years.[10,11] However, empirical research indicates variation in practice, which is reflected in the wide range of frequencies of sedation practices reported.[4–13] Available evidence indicates that this variation is not only partly associated with differences in the care settings, patient populations and study methodology, but also with different concepts of 'palliative sedation'.[6,8,14–16] Most empirical data rely on self-reported 'palliative sedation' by the healthcare team, and most refer to 'continuous (deep) sedation (until death)'.[5,6,8–12,16–20] However, the term 'palliative sedation' includes a range of different types of sedation, and there is a lack of consensus regarding the definition of 'palliative sedation'.[3,14,21–24] This is also reflected in the heterogeneity of the international guidelines' definitions of 'palliative sedation'.[24–27] Controversial aspects include a differentiation between '(primary) palliative sedation' and 'secondary sedation', when sedation is not primarily intended, but a side effect of symptom-oriented therapy, for example, the treatment of hyperactive delirium.[2,6,12,28,29] In conclusion, most previous studies rely on 'palliative sedation' labelled as such by the healthcare team, and there is no consensus regarding the question when the use of sedatives represents 'palliative sedation'.

We aimed to assess the use and labelling of 'continuous administration of sedatives within the last 7 days of life', based on objective operational criteria, on a palliative care unit (PCU). Objectives were to describe and compare clinical and sociodemographic characteristics of (1) patients with or without 'continuous administration of sedatives within the last 7 days of life' and (2) patients with or without the label '(palliative) sedation' for this therapy.

Methods

A retrospective cohort study of patients who died on a German PCU (urban university hospital) between August 2014 and July 2015 was conducted, based on the medical records.

Based on the literature, we developed a data extraction tool, refined it together with expert PCU pharmacists and piloted it using 10 medical records.[3,17,28,30,31] We recorded the use of the following sedatives recommended for 'palliative sedation': benzodiazepines, levomepromazine, haloperidol $\geqslant$5 mg/day (as lower doses are unlikely to be sedating; in recent guidelines, only recommended for 'palliative sedation' for delirium in combination with midazolam) and propofol.[1,3,25,32–35] The administration of levomepromazine or haloperidol with the indication 'nausea/vomiting' was not recorded. The use of opioids was not recorded as they are not used for sedation on the respective PCU, ascertained by regular specialist ward rounds and ongoing training. The definition of 'continuous administration' was based on the available literature and consensus by PCU pharmacists and clinicians as either continuous parenteral infusion for at least 0.5 h or regular intermittent administration resulting in a continuous blood level of the sedative for at least 24 h: for levomepromazine and haloperidol one dose, for lorazepam two doses per 24 h.[13,33] We applied these objective operational criteria to describe the use of sedatives that would comply with the definitions of continuous or intermittent 'palliative sedation', regardless of the labelling of the therapy as such in the medical records.[3,36] Indications for sedative use were extracted from the drug sheet, the

physicians' documentation or the discharge letter. Symptoms had been documented in the medical records using the Integrated Palliative care Outcome Scale (IPOS).[37] For data analysis, in accordance with previous studies, the documented presence or absence of a symptom was recorded at admission to the PCU, on the day before death and on the day of death.[17] The nurses' daily documentation was used plus the IPOS to determine the presence or absence of anxiety and/or agitation.

Data extraction was performed by S.P. and checked by an independent second researcher (L.F.) for randomly selected 25% of all medical records and for the 22 patients with documentation of the terms '(palliative) sedation'.

Explorative statistical analysis was conducted using SPSS 23. Medians and minimums of drug doses were determined for all patients who received the drug on the respective day(s), that is, excluding dose values of 0 mg. The frequency of symptoms is reported in 'valid percent', that is, based on the number of patients for whom the presence or absence of the respective symptom was documented. Group differences regarding nominal or ordinal data were tested using the chi-square test, regarding metric data using the Mann–Whitney *U* test. Alpha level was set at 0.05.

The study was approved by the research ethics committee of Ludwig-Maximilians-Universitaet Munich (reference number 322-15; 15 June 2015).

Results

A total of 208 patients died on the PCU between August 2014 and July 2015. Medical records of 16 of these were missing in the archive for unknown reasons. No indication for bias was detectable. The 192 deceased patients whose data could be extracted from the records had a median age of 72 years (range, 16–95 years), 94 (49%) were male, and 148 (77%) had malignant disease as the main diagnosis (see Table 1).

Continuous administration of sedatives

Out of the 192 patients, 149 (78%) received continuous sedatives within the last 7 days of life. The most frequent indications were agitation (51 patients; 34%) and anxiety (40 patients; 27%), others were delirium (9 patients; 6%), the use as anticonvulsive drug (8 patients; 5%, in addition to the indication agitation or anxiety), dyspnoea (7 patients; 5%) and sleep disorder (4 patients; 3%, in addition to the indication agitation or anxiety). More than one indication was documented for 25 patients (17%) and none for 53 patients (36%). The median duration of continuous administration of sedatives was 2.3 days (range, 0.5 h to 16.2 days). Two patients only received the therapy on the penultimate day of life; the therapy was continued until death for all others. Midazolam was used most frequently (145 patients; 97%), followed by haloperidol (18 patients; 12%) and levomepromazine (4 patients; 3%), mostly in combination with midazolam. Propofol was not used in the study period. Two continuous sedatives were used simultaneously for 19 patients: 14 patients received haloperidol, 3 levomepromazine and 2 lorazepam continuously in addition to midazolam. The number of patients who received continuous sedatives increased towards death. The median total daily dose of midazolam only slightly increased from 6 days before death onwards and was 12.5 (range, 2.0–240.0) mg on the day of death.

Patients with continuous sedatives had a significantly higher prevalence of delirium or agitation at admission to the PCU and on the day before death and a significantly smaller prevalence of nausea and of vomiting on the day of death compared to patients without continuous sedatives. Survival after admission to the PCU was significantly longer in patients with continuous sedatives. The groups did not differ significantly regarding age, gender, main diagnosis (malignant vs non-malignant), functional status at admission according to the Australia-modified Karnofsky Performance Status (AKPS)[38] and the prevalence of anxiety, pain or dyspnoea (Table 1).

Labelling of the continuous administration of sedatives

The term 'sedation' or 'palliative sedation' was documented for 22 of 149 patients (15%) with continuous sedatives in the medical records (11% of the 192 patients who died in the study period). 'Palliative sedation' was documented for two patients (1% of the 192 patients who died in the study period). The most frequently documented indications for the therapy labelled 'sedation' were agitation (11 patients), anxiety (4 patients) and the wish for sedation (3 patients). The patient and/or the relatives expressed the wish for sedation in 11 cases, and the therapy was primarily suggested by the healthcare team in the remaining 11 cases. All patients with documentation of 'sedation' received continuous midazolam. The median dose increased from 6 days before death (median, 10.0 mg; range, 7.5–80.0 mg) until the penultimate day (median, 20.5 mg; range, 1.0–210.0 mg), with a slight decrease on the day of death (median, 19.5 mg; range, 7.5–240.0 mg; Figure 1(a)). The two patients whose therapy was labelled 'palliative sedation' had maximum total daily doses of midazolam within the last 7 days of life of 58.0 and 135.0 mg. The maximum total daily dose of midazolam within the last 7 days of life was at least 60.0 mg for three additional patients with the therapy labelled 'sedation'. Maximum total daily midazolam doses of 60.0 mg or higher (maximum 80.0 mg) were also given to 5 of 123 patients with continuous midazolam without the label 'sedation' (Figure 1(b)). Depth of sedation was not consistently documented.

Table 1. Comparison of the sociodemographic and clinical characteristics of patients with and without continuous application of sedatives.

	Patients without continuous application of sedatives $n = 43$		Patients with continuous application of sedatives $n = 149$		*p*-value
	n	%	*n*	%	
Age (median (range))	71 (46–95)		72 (16–94)		0.66
Gender					
Male	18	42	76	51	0.31
Female	25	58	73	49	
Main diagnosis					
Malignant disease	36	84	112	75	0.31
Functional Status (AKPS) at admission to the PCU (%) (median (range))	30 (10–60)		30 (10–80)		0.27
Prevalence of delirium/agitation[a]					
Admission to the PCU	7	16	52	35	**0.02**
Day before the day of death	17	40	86	58	**0.04**
Day of death	14	33	72	48	0.08
Prevalence of anxiety[a]					
Admission to the PCU	3	7	29	19	0.06
Day before the day of death	4	9	27	18	0.24
Day of death	6	14	18	12	0.79
Prevalence of pain					
Admission to the PCU	32 (2 missing)	78	104 (16 missing)	78	1.00
Day before the day of death	18 (3 missing)	45	82 (7 missing)	58	0.21
Day of death	20 (7 missing)	56	64 (31 missing)	54	1.00
Prevalence of dyspnoea					
Admission to the PCU	23 (3 missing)	58	79 (23 missing)	63	0.58
Day before the day of death	21 (18 missing)	84	72 (44 missing)	69	0.15
Day of death	16 (22 missing)	76	62 (63 missing)	72	0.79
Prevalence of nausea					
Admission to the PCU	22 (4 missing)	56	53 (29 missing)	44	0.20
Day before the day of death	11 (15 missing)	39	21 (69 missing)	26	0.23
Day of death	10 (22 missing)	48	6 (104 missing)	13	**<0.01**
Prevalence of vomiting					
Admission to the PCU	14 (2 missing)	34	30 (31 missing)	25	0.31
Day before the day of death	9 (6 missing)	24	13 (25 missing)	11	0.05
Day of death	5 (11 missing)	16	4 (47 missing)	4	**0.04**
Survival after admission to the PCU (days; median (range))	4.0 (0–20)		6 (0–28)		**0.01**
Average cumulative dose of midazolam per day spent on the PCU within the last 7 days of life[b] (mg; median[c] (range))	1.1 (0.2–33.0)		11.3 (1.0–157.1)		**<0.01**
Application of other sedatives, as continuous monotherapy or in addition to midazolam, either continuously or intermittently 'as needed'					
Haloperidol	1	2	19	13	0.05
Lorazepam	16	37	65	44	0.49
Levomepromazine	0	0	6	4	0.34

AKPS: Australia-modified Karnofsky Performance Status; PCU: palliative care unit.
Bold numbers: significant results (α-level 0.05).
The frequency of symptoms is reported in 'valid percent', that is, based on the number of patients for whom the presence or absence of the respective symptom is documented.
[a]In contrast to the other symptoms, delirium/agitation and anxiety were documented for all patients on the days studied, without any missing values.
[b]Cumulative dose of midazolam during the last 7 days of life, divided by the number of days spent on the PCU within this time.
[c]Median and minimum of drug doses were determined for all patients who received the drug on the respective day(s), that is, dose values of 0 mg were excluded.

Patients with documentation of 'sedation' had a significantly higher prevalence of pain on the day of death and a significantly smaller prevalence of nausea at admission than the patients without documentation of

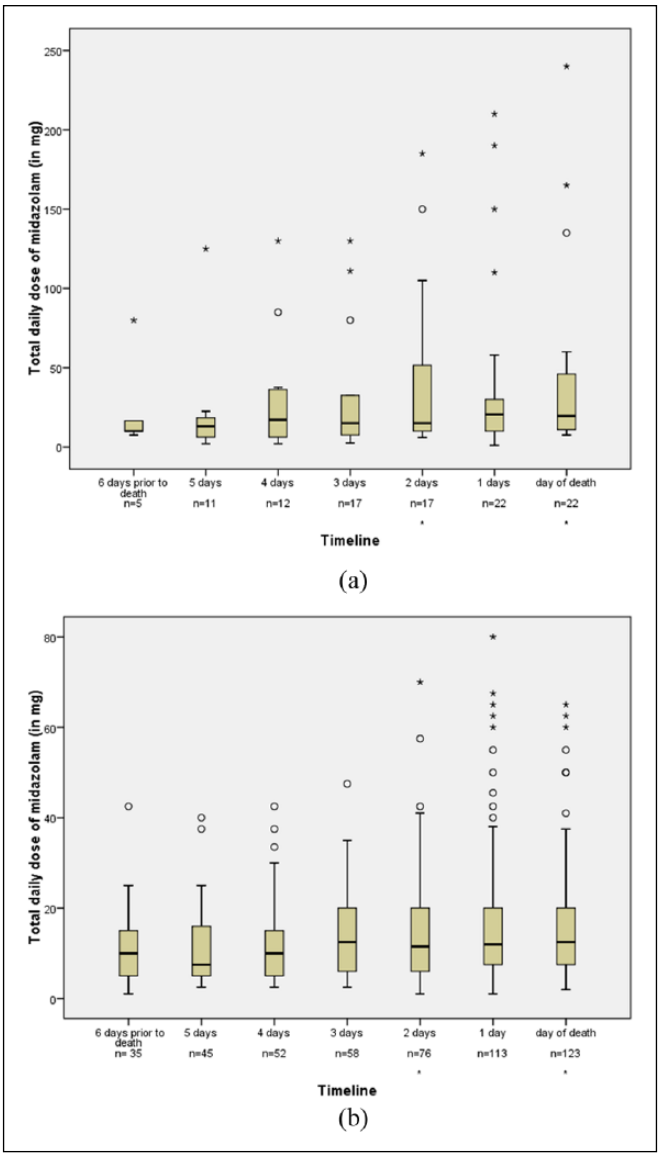

Figure 1. Total daily dose of midazolam over the last 7 days of life for the patients with continuous administration of midazolam: (a) with documentation of the term 'sedation' ($n = 22$) and (b) without documentation of the term 'sedation' ($n = 123$) (Mind: different scale on the y-axis compared to Figure 1(a)).

*Under boxplots: significant differences between the groups of patients with and without documentation of the term 'sedation': Total daily midazolam dose 2 days before death: median (range) 15.0 (6.0–185.0) mg versus 11.5 (1.0–70.0) mg, $p = 0.04$.

Total daily midazolam dose on the day of death: median (range) 19.5 (7.5–240.0) mg versus 12.5 (2.0–65.0) mg, $p = 0.01$.

Boxplots:

Bottom of the box: first quartile; top of the box: third quartile; band inside the box: median; 'whiskers' with maximum 1.5 × interquartile range.

°Mild outliers: lying between 1.5 and 3 × interquartile range.

*Extreme outliers: lying beyond 3 × interquartile range.

this term. The total daily doses of midazolam 2 days before death and on the day of death were significantly higher in the group of patients with documentation of 'sedation' than in the group without this label for the therapy, with large dose ranges in both groups (median (range), 19.5 (7.5–240.0) mg vs 12.5 (2.0–65.0) mg, $p = 0.01$, on the day of death). Compared with the patients without documentation of 'sedation', patients with documentation of this term were also significantly more frequently given levomepromazine in addition to midazolam. The groups did not differ significantly regarding age; gender; main diagnosis (malignant vs non-malignant); functional status according to the AKPS at admission; prevalence of agitation, anxiety, dyspnoea or vomiting; survival after admission to the PCU; duration of continuous administration of sedatives; or the total daily doses of midazolam 6, 5, 4, 3 and 1 day before death (Table 2, Figure 1(a) and (b)).

Table 2. Comparison of the sociodemographic and clinical characteristics of patients with and without documentation of the term 'sedation' in the medical records for the continuous administration of sedatives.

	Patients with 'sedation' *n* = 22		Patients without 'sedation' *n* = 127		*p*-value
	n	%	*n*	%	
Age (median (range))	71 (37–84)		72 (16–94)		0.82
Gender					
Male	9	41	67	53	0.36
Female	13	59	60	47	
Main diagnosis					
Malignant disease	18	82	94	74	0.60
Functional Status (AKPS) at admission to the PCU (%; median (range))	40 (10–70)		30 (10–80)		0.18
Prevalence of delirium/agitation[a]					
Admission to the PCU	9	41	43	34	0.63
Day before the day of death	16	73	70	55	0.16
Day of death	12	55	60	47	0.65
Prevalence of anxiety[a]					
Admission to the PCU	6	27	23	18	0.38
Day before the day of death	6	27	21	17	0.24
Day of death	5	23	13	10	0.15
Prevalence of pain					
Admission to the PCU	19	86	85 (16 missing)	77	0.41
Day before the day of death	14 (2 missing)	70	68 (5 missing)	56	0.33
Day of death	14 (4 missing)	78	50 (27 missing)	50	**0.04**
Prevalence of dyspnoea					
Admission to the PCU	14 (1 missing)	67	65 (22 missing)	62	0.81
Day before the day of death	13 (6 missing)	81	59 (38 missing)	67	0.38
Day of death	13 (8 missing)	93	49 (55 missing)	68	0.10
Prevalence of nausea					
Admission to the PCU	4 (1 missing)	19	49 (28 missing)	50	**0.02**
Day before the day of death	3 (8 missing)	21	18 (61 missing)	27	0.75
Day of death	1 (15 missing)	14	5 (89 missing)	13	1.00
Prevalence of vomiting					
Admission to the PCU	2 (1 missing)	10	28 (30 missing)	29	0.10
Day before the day of death	3 (2 missing)	15	10 (23 missing)	10	0.44
Day of death	1 (6 missing)	6	3 (41 missing)	4	0.50
Survival after admission to the PCU (days; median (range))	6.5 (1–23)		6 (0–28)		0.34
Duration of the continuous application of sedatives (days) on the PCU (median (range))	4.00 (0.10–13.30)		2.00 (0.02–16.20)		0.25
Average cumulative dose of midazolam per day spent on the PCU within the last seven days of life[b] (mg; median[c] (range))	14.9 (1.8–157.1)		11.1 (1.0–85.0)		0.14
Application of other sedatives, as continuous monotherapy or in addition to midazolam, either continuously or intermittently 'as needed'					
Haloperidol	2	9	17	13	0.74
Lorazepam	13	59	52	41	0.16
Levomepromazine	3	14	3	2	**0.04**
Diazepam	1	5	0	0	–

AKPS: Australia-modified Karnofsky Performance Status; PCU: palliative care unit.

Bold numbers: significant results (α-level 0.05).

The frequency of symptoms is reported in 'valid percent', that is, based on the number of patients for whom the presence or absence of the respective symptom is documented.

[a]In contrast to the other symptoms, delirium/agitation and anxiety were documented for all patients on the days studied, without any missing values.

[b]Cumulative dose of midazolam during the last 7 days of life, divided by the number of days spent on the PCU within this time.

[c]Median and minimum of drug doses were determined for all patients who received the drug on the respective day(s), that is, dose values of 0 mg were excluded.

Discussion

Main results

This study describes the continuous use of sedatives in the last 7 days of life on a PCU adopting objective operational criteria and characterizes this practice, to the best of our knowledge for the first time, with reference to the label '(palliative) sedation'.

The main findings are, first, that most patients who died on the PCU during 1 year received continuous sedatives in mid ranges within the last week of life, and that the use of sedatives was associated with the prevalence of delirium/agitation, consistent with these symptoms being the most frequent indications for this treatment. Second, the term 'sedation' was only documented for a minority of the patients with continuous sedatives. Third, patients with documentation of the label 'sedation' had significantly higher doses of midazolam 2 days before death and on the day of death. However, the range of dose was large in both groups, and there was no consistent pattern overall regarding labelling the use of continuous sedatives as 'sedation'.

Continuous administration of sedatives

Almost four in five patients who died on the PCU received continuous sedatives within the last 7 days of life, mostly midazolam. This is comparable with the data from the United Kingdom, where 69% of patients in a hospital support team and a hospice received sedatives, either 'to sedate them' (26%) or for 'symptom control' (43%), the distinction between the two aims being made by the researchers on reviewing the case notes.[31] By contrast, a previous German study reported that only 3.1% of the 160 patients treated on a PCU within the study period received midazolam continuously. However, this study assessed not only patients who died on the unit, but all treated on the PCU, included no other sedatives besides benzodiazepines and did not report the percentage of patients with regular application of oral benzodiazepines.[28] The median duration of continuous application of sedatives of 2.3 days in our study sample is comparable with a recent study of 'sedation practice' on Austrian PCUs.[13] By contrast, other studies reporting practice labelled 'palliative sedation' report a shorter median duration of sedation of around 24 h.[12,17] The depth of sedation was not consistently documented. The median total dose on the day of death of 12.5 mg is usually maximally mildly sedating, with maintained ability to communicate.

Agitation was one of the most frequently documented indications for the administration of continuous sedatives, as in studies describing 'palliative sedation'.[8,9,12,17,31] Accordingly, there was an association between the use of continuous sedatives and the prevalence of delirium or agitation. The finding that survival after admission to the PCU was significantly longer in patients with continuous sedatives than in the group without adds to the growing evidence that the use of sedatives is not associated with a shortened survival.[8,17,30]

Labelling of the continuous administration of sedatives

This therapy was labelled 'palliative sedation' for only two patients with continuous sedatives. Similarly, this term was applied for none of the five patients with continuous midazolam application in the German study of benzodiazepine use previously mentioned; however, all were labelled 'sedation'.[28] In our study sample, the continuous administration of sedatives was labelled 'sedation' for only 15% of patients with continuous application of sedatives, corresponding to 11% of the patients who died in the study period. This is a lower frequency than in recent studies of 'palliative sedation' at the end of life of, for example, 34% on a German PCU or 21% on Austrian PCUs, but lies within the wide range of frequency of 'palliative sedation' reported in previous studies.[5,6,8–10,12,13,18,39]

Comparable to previous studies reporting the practice of 'palliative sedation', agitation and anxiety were among the most frequently documented indications for the therapy labelled 'sedation'.[8,9,12,17] Interestingly, 'wish for sedation' was documented as indication in three cases. This raises the question whether sedation can be a wish-fulfilling therapy and on which basis limits to such wishes can be justified.[40]

Variables associated with the label 'sedation' for the continuous administration of sedatives were the prevalence of pain on the day of death, the application of levomepromazine in addition to midazolam and the dose of midazolam 2 days before and on the day of death. The higher dose of midazolam and the more frequent addition of levomepromazine in patients with the label 'sedation' could – in the absence of data on depth of sedation – suggest that physicians are more likely to label deep sedation as 'sedation' and to regard the application of lower doses of sedatives as 'symptom control with secondary sedation'. This would be in accordance with the findings from, for example, the United Kingdom.[16] However, there were no significant differences in the dose of midazolam between the groups with and without the label 'sedation' on days other than the penultimate day before death and the day of death, and there were large ranges of dose in both groups. Besides, the continuous administration of sedatives was labelled as 'sedation' for only four of nine patients, with maximum total daily doses of midazolam $\geqslant$60.0 mg, a dose which is well within or even above the maintenance dose range recommended for 'palliative sedation' and usually causes at least moderate sedation.[1,3] No consistent pattern was detected overall, regarding when the continuous administration

of sedatives was labelled 'sedation'. This suggests that variables that were not assessed influence the labelling of this practice, such as the documenting physician's concept of 'sedation'.

Strengths and limitations

This was a retrospective study with all limitations of a retrospective design, including missing medical records and missing information, for example, regarding the indication and intention of the use of sedatives and level of sedation. However, the reason for choosing this design was that knowing about an ongoing prospective study could have influenced the decisions of the healthcare team and the labelling of the treatment practice.[30] Another main limitation is that the data in this exploratory study were acquired from a single centre and are, therefore, not generalizable. The numbers of studied patients are, however, comparable to or higher than similar mono-centre studies.[12,17,28,30] As this was an exploratory study, we did not correct *p*-values for multiple testing. Significant results have to be interpreted considering this.

The main strengths of this study are that it is not limited to 'continuous deep sedation', as many international studies are.[8,10,11,16–20] Furthermore, it adopts objective operational criteria to assess the use of sedatives regardless of the labelling of the practice by the healthcare team. The few existing studies with a similar approach either only assessed benzodiazepines or used cut-off points for 'sedating' drug doses that were considered too high by our expert clinicians and pharmacists in light of the recommended dosage in the literature.[3,25,28,30,32–34] Finally, it is the first study that assessed which variables might influence the labelling of the use of sedatives by the healthcare team. In all three respects, this study's methods and results can serve as a starting point for future, multicentre research.

Conclusion and implications for clinical practice and further research

Continuous administration of sedatives was performed frequently within the last week of life in this study. Comparable use of sedatives (e.g. regarding dose and indication) was only partly labelled 'sedation', and there was no consistent pattern regarding the use of this label for the continuous administration of sedatives. Such lack of consistency is relevant for future research and clinical practice. Regarding research, current heterogeneous data on self-reported 'palliative sedation' practice may be due to differing labelling of comparable practices. In clinical practice, not labelling the continuous use of sedatives at the end of life as 'sedation' may result in failure of compliance with existing guidelines on 'palliative sedation'.

Multicentre quantitative and qualitative empirical research and conceptual analysis are needed for a better understanding and characterization of sedation practices and their labelling in palliative care. Based on such analyses, consensus for defining different types of sedation and their differentiation from 'symptom control with secondary sedation' should be sought. Such consensus is needed (1) for policy makers to further refine the existing guidelines on 'palliative sedation', (2) for practitioners to know when to apply guidelines for 'palliative sedation' and (3) for researchers to generate empirical results that are comparable to other studies – to further promote best practice of sedation in palliative care.

Acknowledgements

We thank our expert PCU pharmacists (C. Remi and D. Bauer) for their valuable input regarding the definition of sedating doses and intervals of drug application which result in a continuous blood level of the respective sedatives. We also thank L. Fischer for checking the data extraction for part of the medical records as an independent second researcher.

Availability of data and material

The data on which the findings of this study are based were used under the data agreement for this study (ethics approval by Ludwig-Maximilians-Universitaet Munich, reference number 322-15; 15 June 2015) and so are not publicly available. They are available for the authors under the provision that the research ethics committee of the Ludwig-Maximilians-Universitaet agrees.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: E.S.'s work is supported by the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung (BMBF); Grant project number: 01GY1712, 'Sedation at the end of life outside specialist palliative care. An exploratory mixed-methods study on practices and challenges in Germany (SedEol)').

References

1. de Graeff A and Dean M. Palliative sedation therapy in the last weeks of life: a literature review and recommendations for standards. *J Palliat Med* 2007; 10: 67–85.
2. Dean MM, Cellarius V, Henry B, et al. Framework for continuous palliative sedation therapy in Canada. *J Palliat Med* 2012; 15: 870–879.
3. Cherny NI and Radbruch L. European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. *Palliat Med* 2009; 23: 581–593.

4. Muller-Busch HC, Andres I and Jehser T. Sedation in palliative care – a critical analysis of 7 years experience. *BMC Palliat Care* 2003; 2: 2.
5. Jaspers B, Nauck F, Lindena G, et al. Palliative sedation in Germany: how much do we know? A prospective survey. *J Palliat Med* 2012; 15: 672–680.
6. Klosa PR, Klein C, Heckel M, et al. The EAPC framework on palliative sedation and clinical practice – a questionnaire-based survey in Germany. *Support Care Cancer* 2014; 22: 2621–2628.
7. Schildmann J, Dahmen B and Vollmann J. Ärztliche Handlungspraxis am Lebensende. *Dtsch Med Wochenschr* 2015; 140: e1–e6.
8. Maltoni M, Scarpi E, Rosati M, et al. Palliative sedation in end-of-life care and survival: a systematic review. *J Clin Oncol* 2012; 30: 1378–1383.
9. Beller EM, van Driel ML, McGregor L, et al. Palliative pharmacological sedation for terminally ill adults. *Cochrane Database Syst Rev* 2015; 1: CD010206.
10. Bosshard G, Zellweger U, Bopp M, et al. Medical end-of-life practices in Switzerland: a comparison of 2001 and 2013. *JAMA Intern Med* 2016; 176: 555–556.
11. Van der Heide A, van Delden JJM and Onwuteaka-Philipsen BD. End-of-life decisions in the Netherlands over 25 years. *N Engl J Med* 2017; 377: 492–494.
12. Hopprich A, Gunther LD, Laufenberg-Feldmann R, et al. Palliative sedation at a university palliative care unit – a descriptive analysis. *Dtsch Med Wochenschr* 2016; 141: e60–e61.
13. Schur S, Weixler D, Gabl C, et al. Sedation at the end of life – a nation-wide study in palliative care units in Austria. *BMC Palliat Care* 2016; 15: 50.
14. Papavasiliou ES, Brearley SG, Seymour JE, et al. From sedation to continuous sedation until death: how has the conceptual basis of sedation in end-of-life care changed over time? *J Pain Symptom Manage* 2013; 46: 691–706.
15. Morita T. Differences in physician-reported practice in palliative sedation therapy. *Support Care Cancer* 2004; 12: 584–592.
16. Seymour J, Rietjens J, Bruinsma S, et al. Using continuous sedation until death for cancer patients: a qualitative interview study of physicians' and nurses' practice in three European countries. *Palliat Med* 2015; 29: 48–59.
17. Rietjens JAC, van Zuylen L, van Veluw H, et al. Palliative sedation in a specialized unit for acute palliative care in a cancer hospital: comparing patients dying with and without palliative sedation. *J Pain Symptom Manage* 2008; 36: 228–234.
18. Miccinesi G, Rietjens JA, Deliens L, et al. Continuous deep sedation: physicians' experiences in six European countries. *J Pain Symptom Manage* 2006; 31: 122–129.
19. Robijn L, Cohen J, Rietjens J, et al. Trends in continuous deep sedation until death between2007 and 2013: a repeated nationwide survey. *PLoS ONE* 2016; 11: e0158188.
20. Rietjens JA, Buiting HM, Pasman HR, et al. Deciding about continuous deep sedation: physicians' perspectives: a focus group study. *Palliat Med* 2009; 23: 410–417.
21. Alt-Epping B, Nauck F and Jaspers B. Was ist das Problematische an der Palliativen Sedierung? – eine Übersicht. *Ethik Med* 2015; 3: 219–231.
22. Morita T, Maeda I, Mori M, et al. Uniform definition of continuous-deep sedation. *Lancet Oncol* 2016; 17: e222.
23. Morita T, Imai K, Yokomichi N, et al. Continuous deep sedation: a proposal for performing more rigorous empirical research. *J Pain Symptom Manage* 2017; 53: 146–152.
24. Schildmann E and Schildmann J. Palliative sedation therapy: a systematic literature review and critical appraisal of available guidance on indication and decision making. *J Palliat Med* 2014; 17: 601–611.
25. Schildmann EK, Schildmann J and Kiesewetter I. Medication and monitoring in palliative sedation therapy: a systematic review and quality assessment of published guidelines. *J Pain Symptom Manage* 2015; 49: 734–746.
26. Abarshi E, Rietjens J, Robijn L, et al. International variations in clinical practice guidelines for palliative sedation: a systematic review. *BMJ Support Palliat Care* 2017; 7: 223–229.
27. Gurschick L, Mayer DK and Hanson LC. Palliative sedation: an analysis of international guidelines and position statements. *Am J Hosp Palliat Care* 2015; 32: 660–671.
28. Stiel S, Krumm N, Schroers O, et al. Indications and use of benzodiazepines in a palliative care unit. *Schmerz* 2008; 22: 665–671.
29. Maiser S, Estrada-Stephen K, Sahr N, et al. A survey of hospice and palliative care clinician's experiences and attitudes regarding the use of palliative sedation. *J Palliat Med* 2017; 20: 915–921.
30. Sykes N and Thorns A. Sedative use in the last week of life and the implications for end-of-life decision making. *Arch Intern Med* 2003; 163: 341–344.
31. Stone P, Phillips C, Spruyt O, et al. A comparison of the use of sedatives in a hospital support team and in a hospice. *Palliat Med* 1997; 11: 140–144.
32. Morita T, Bito S, Kurihara Y, et al. Development of a clinical guideline for palliative sedation therapy using the Delphi method. *J Palliat Med* 2005; 8: 716–729.
33. Remi C, Bausewein C, Twycross R, et al. *Arzneimitteltherapie in der Palliativmedizin*. München: Urban & Fischer, 2015.
34. Watson M, Lucas C, Hoy A, et al. *Oxford handbook of palliative care*, 2nd ed. Oxford: Oxford University Press, 2009.
35. Twycross R, Wilcock A and Howard P. Palliativedrugs.com Ltd, www.palliativedrugs.com (accessed 8 July 2014).
36. Kirk TW and Mahon MM. National Hospice and Palliative Care Organization (NHPCO) position statement and commentary on the use of palliative sedation in imminently dying terminally ill patients. *J Pain Symptom Manage* 2010; 39: 914–923.
37. Schildmann EK, Groeneveld EI, Denzel J, et al. Discovering the hidden benefits of cognitive interviewing in two languages: the first phase of a validation study of the integrated palliative care outcome scale. *Palliat Med* 2016; 30: 599–610.
38. Abernethy AP, Shelby-James T, Fazekas BS, et al. The Australia-modified Karnofsky Performance Status (AKPS) scale: a revised scale for contemporary palliative care clinical practice [ISRCTN81117481]. *BMC Palliat Care* 2005; 4: 7.
39. Onwuteaka-Philipsen BD, Brinkman-Stoppelenburg A, Penning C, et al. Trends in end-of-life practices before and after the enactment of the euthanasia law in the Netherlands from1990 to 2010: a repeated cross-sectional survey. *Lancet* 2012; 380: 908–915.
40. Bozzaro C. The concept of suffering in medicine: an investigation using the example of deep palliative sedation at the end of life. *Ethik Med* 2015; 2015: 1–14.