

Original Article

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Comparison of inpatient and outpatient palliative sedation practice – A prospective observational study

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Abstract

Introduction. Palliative sedation (PS) is an intrusive measure to relieve patients at the end of their life from otherwise untreatable symptoms. Intensive discussion of the advantages and limitations of palliative care with the patients and their relatives should precede the initiation of PS since PS is terminated by the patient's death in most cases. Drugs for PS are usually administered intravenously. Midazolam is widely used, either alone or in combination with other substances. PS can be conducted in both inpatient and outpatient settings; however, a quality analysis comparing both modalities was missing so far.

Patients and methods. This prospective observational study collected data from patients undergoing PS inpatient at the palliative care unit (PCU, $n = 26$) or outpatient at a hospice ($n = 2$) or at home (specialized outpatient palliative care [SAPV], $n = 31$) between July 2017 and June 2018. Demographical data, indications for PS, and drug protocols were analyzed. The depth of sedation according to the Richmond Agitation Sedation Scale (RASS) and the degree of satisfaction of staff members and patient's relatives were included as parameters for quality assessment.

Results. Patients undergoing PS at the PCU were slightly younger compared to outpatients (hospice and SAPV combined). Most patients suffered from malignant diseases, and midazolam was the backbone of sedation for inpatients and outpatients. The median depth of sedation was between +1 and –3 according to the RASS with a trend to deeper sedation prior to death. The median degree of satisfaction was “good,” scored by staff members and by patient's relatives. Significant differences between inpatients and outpatients were not seen in protocols, depth of sedation, and degree of satisfaction.

Conclusion. The data support the thesis that PS is possible for inpatients and outpatients with comparable results. For choosing the best place for PS, other aspects such as patient's and relative's wishes, stress, and medical reasons should be considered.

Introduction

Palliative sedation (PS) is the therapeutic induction of sedation, resulting in loss of consciousness in patients suffering from otherwise uncontrollable symptoms in their last and very limited phase of life (Cherny and Radbruch 2009). This concept has been initially published by Enck as “terminal sedation” (Enck 1991). Possible indications for a PS are, for example, pain, dyspnea, seizures, delirium, anxiety, and other symptoms that cannot be controlled by a specific therapeutic measure. Such refractory symptoms occur in 5% up to 35% of palliative care patients (Benítez-Rosario and Belén 2020; LiPuma and DeMarco 2016). The initiation of PS requires a mutual relationship between the palliative care physician and the patient or the patient's caregiver because the PS will not be discontinued until death in the majority of cases.

Comprehensive information about the diagnosis, prognosis, and informed consent is mandatory. Further preconditions are an experienced team and close monitoring of the patient (Belar et al. 2020). Several ethical questions have been discussed in the context of PS (Committee and Administration 2006; Rady and Verheijde 2010; Takla et al. 2020). Current consensus guidelines highlight a clear border between PS and assisted death or euthanasia (Materstvedt 2020; Rady and Verheijde 2010).

Most frequent indication for PS is delirium followed by pain dyspnea and psychological/existential distress (Arantzamendi et al. 2020). Common drugs used for PS are benzodiazepines, neuroleptics, barbiturates, and propofol (Arantzamendi et al. 2020).

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Table 1. Characteristics of PCU, hospice, and SAPV

Setting/features	PCU	Hospice	SAPV
Physician availability	Residents and PC physicians, 24/7 availability	GP and PC physicians, regular visits and on demand, visit interval upon necessity	GP and PC physicians, regular visits and on demand, visit interval upon necessity
Nursing staff	24/7 presence	Volunteer nurses and/or nonprofessional volunteers, 24/7 presence. SAPV team, regular visits (when PS is running), visit interval upon necessity	Regular visits and on demand, visit interval upon necessity
Presence of trained hospital (PCU) staff	Yes	No	No
Primary care by caregivers/relatives	Uncommon but possible	Uncommon but possible	Yes

Note: PC, palliative care; GP, general practitioner; PCU, palliative care unit; SAPV, specialized outpatient palliative care service; and 24/7, around the clock 7 days per week.

Despite the existence of national and international guidelines for PS, institutional guidelines are often lacking (Gurschick *et al.* 2015; Schur *et al.* 2016). Furthermore, a close monitoring and an assessment of patients undergoing PS is necessary (Brinkkemper *et al.* 2013).

To evaluate the current practice of PS in Pomerania and to compare the practice between inpatients at a palliative care unit (PCU) and outpatients at home or in a hospice, this prospective observational study was conducted.

In most cases, PS will be pursued until the death of the patient. Since the patients and their relatives often have preferences, which is the best place to spend the last episode of life – on a PCU, in a hospice, or at home – a PS procedure should be practicable at any of these sites. This prospective observational trial should contribute to the clarification of the following questions:

1. Can PS only be conducted in the setting of a hospital or can it also be conducted outside the hospital in a hospice or in another outpatient care concept?
2. Are there significant differences in the indications for PS and in the operational implementation between the PCU and the outpatient setting?
3. Can a PS procedure outside a PCU deliver a comparable quality and satisfaction compared to that on a PCU with a 24/7 presence of specialized medical staff members?

Patients and methods

General aspects

The present study was conducted as a prospective noninterventional observational investigation. The trial was approved by the ethics committee of Greifswald University on June 27, 2017 (<http://www2.medizin.uni-greifswald.de/ethik>). The investigation was noninterventional and followed the declaration of Helsinki. The data were collected between July 2017 and June 2018. The involved institutions were the PCU of Greifswald University Hospital, the hospice of Greifswald, and the specialized outpatient palliative care (SAPV) service of Greifswald-Pomerania. Participants were the staff members, patients of at least one of the institutions, and the patients' relatives. The investigators were not involved in the patient's treatment or in any medical decision.

For outpatient PS at home, it was mandatory that at least one relative or caregiver lived in the same household as the patient. The major differences between a PCU, a hospice, and an SAPV are shown in Table 1. The PS in the hospice and at home was always carried out by an SAPV team.

Definition of palliative sedation

Any sedation reducing the consciousness with the intention to reduce otherwise refractory symptoms was interpreted as a PS. This definition included terminal sedations at the end of life and intermittent sedations that were discontinued after successful control of intolerable symptoms by other measures.

Data collection

The total number of patients and the number of patients receiving a PS treated by each institution in the observational interval were documented. Basic data were patient's age, gender, underlying diagnosis with time of diagnosis, performance score (Eastern Cooperative Oncology Group [ECOG]), prior palliative care treatment (when applicable), family status, children, support by caregivers at home, and prior profession of the patient. Additionally, data from the informed consent form were included in the analysis (Young *et al.* 2015). The informed consent had to be completed and signed by the patient's physician, a member of the nursing staff, the patient if possible, and his/her caregiver. On the informed consent, the method and the goal of the planned PS were noted, as well as the planned co-medication, the nutrition, and the liquid substitution.

After the start of the PS, a detailed protocol was conducted. Documentation included used medications, the depth of unconsciousness, the satisfaction of the patient's caregivers and of the staff, and additional medical data at defined time points. The depth of sedation was scored using the established Richmond Agitation Sedation Scale (RASS) (Sessler *et al.* 2002).

It was the goal to assess the depth of sedation and the degree of satisfaction of the staff members and the patient's relatives with the sedation procedures 3 times daily, according to one value per shift. Depth of sedation was assessed following the RASS score, and the degree of satisfaction was scored from 1 (very good) to 6 (poor) based on the grading system for German school marks (Sessler *et al.* 2002). The latter graduation was chosen to facilitate the scoring for the patient's relatives, usually not familiar with medical scores. The analyses were performed with values obtained during the last 5 days prior to the death of the patient.

Data documentation and statistics

Primary documentation was paper based and carried out by staff members of the PCU, by the members of the SAPV team, and by the patient's caregivers, when appropriate. Data were transferred by members of the investigation group to Microsoft-Excel spreadsheets, and statistical analyses were performed using the software

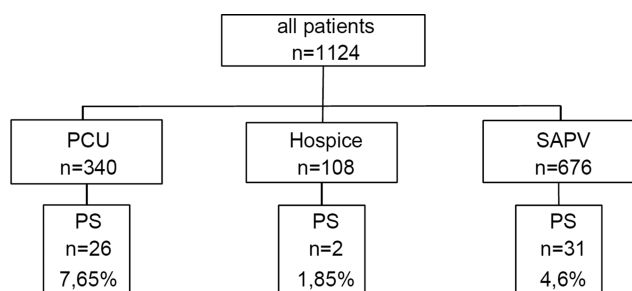


Fig. 1. Study population. PCU, palliative care unit; SAPV, specialized outpatient palliative care; and PS, palliative sedation.

programs SPSS and SAS. Statistical tests used for the analysis are indicated where appropriate.

The demographical data were analyzed using the chi-square test and Fisher's exact test (where indicated). The data sets "depth of sedation" and "satisfaction" were analyzed using McNemar's test.

Results

Patients characteristics

A total of 1,124 patients were treated during the observational period in the PCU ($n = 340$), in the hospice ($n = 108$), and by the outpatient palliative care service ($n = 676$). A total of 756 patients gave their consent to the investigation. Data of these patients were available for detailed analysis.

The percentage of patients that received a PS was 7.7% (PCU, $n = 26$), 1.9% (hospice, $n = 2$), and 4.6% (SAPV, $n = 31$), respectively. The difference between the PCU and the hospice was significant (0.037, Fisher's exact test; [Figure 1](#)). Of all patients, 57.1% were male and 42.9% were female with PS rates of 7.9% and 7.7%, respectively (n.s.).

The mean age of all patients without PS was 71.8 years ($SD = \pm 12.3$ years, range 22–97) compared to 68.1 years ($SD = \pm 13$ years, range 37–91) of patients treated with PS ($p = 0.033$). In detail, this difference was observed in each setting alone (PCU, hospice, and SAPV), but the difference was only significant for the group treated at the PCU ($p = 0.023$; [Table 2](#)).

The underlying disease was a malignancy in 618 of 756 cases (81.7%). The differences between PCU (285/340, 83.3%), hospice (71/90, 78.9%), and SAPV (262/326, 80.4%) were only slight and nonsignificant ([Table 2](#)). The frequency of PS was neither influenced by the diagnosis of a malignancy nor by the presence of metastatic disease (data not shown). The median interval from the primary diagnosis of the underlying disease to the initiation of PS was 13.5 months (range: 0–18 years).

Four hundred thirty-two of 756 (57.1%) patients were male and 324 of 756 (42.9%) were female without significant differences between PCU, hospice, and SAPV. Gender-dependent differences on the frequency of PS were not observed. About 59.4% of all patients were married or had a committed relationship. In $n = 41$ (9.6%) of these patients, a PS was initiated at the end of life compared to $n = 15$ (5.1%) patients not living in a steady relationship ($p = 0.029$). The parameters children versus childlessness and the place of residence of children had no influence on PS. Most of the patients receiving the PS by SAPV at home were supported by their relatives during their last phase of life. Differences in the level of education between patients receiving PS or not could not be detected.

Indications for palliative sedation

The indications for the initiation of a PS are shown in [Table 3](#). More than one answer was allowed. The leading diagnoses in the entire study collective were agitation ($n = 42$, 77.8%), anxiety ($n = 31$, 57.4%), delirium ($n = 29$, 53.7%), a poor quality of life ($n = 24$, 44.4%), and dyspnea and pain (each $n = 22$, 40.7%). A statistical comparison of subgroups was not conducted due to the low numbers of patients. However, it is noteworthy that agitation was an indication for PS in 92.3% of the patients treated in an outpatient setting (SAPV) compared to 65.4% of patients treated in the PCU ([Table 3](#)).

Sedation procedure

The sedation protocols were available for all patients treated at the PCU and at the hospice and for 26 of 31 patients treated by SAPV in an outpatient setting ([Table 4](#)).

The median duration of PS in all patients was 2.5 days with a range from 4 hours to 18 days. Sedation was conducted for less than 24 hours in 12 of 54 patients (22.2%). Eight of these patients were treated at the PCU and 4 patients in an outpatient setting. Nearly two-thirds of patients (34/54, 63.0%) received sedation over 1–7 days. In 8 cases, the sedation lasted longer than 1 week. In 3 patients sedated in the setting of SAPV, the sedation was terminated prior to death. Significant differences in the length of sedation between PCU, hospice, and SAPV were not seen.

Most patients (51/54, 94.4%) received midazolam for sedation protocol, either as a monotherapy ($n = 44$, 81.5%) or in combination with haloperidol, clonidine, and lorazepam (one each). Three patients received a combination of 3 drugs consisting of midazolam and clonidine plus either propofol ($n = 2$) or levomepromazine ($n = 1$). Three patients received a midazolam-free protocol consisting of propofol monotherapy ($n = 1$) or levomepromazine monotherapy ($n = 2$).

Depth of sedation and satisfaction of the staff and of the relatives

The data from the 2 patients sedated in the hospice and from the SAPV patients sedated at home were pooled for these analyses as "outpatients" since the conditions of both settings are very similar ([Table 1](#)).

A total of 338 values from 48 patients were available for analysis regarding the depth of sedation. The satisfaction of the staff and of the relatives could be analyzed with 293 and 132 scores, respectively, from 44 patients each. The lack of some measurements is, among others, owned to the facts that not all patients were sedated over 5 days and that the relatives were usually not present the whole day. The analyzed data are shown in detail in [Table 5](#).

The span of sedation depth varied between 4 and –5, and the sedation seemed to be lighter during the first days with a trend to an intensification from day –2 ([Table 5](#) and [Figure 2](#)). A variate analysis with the median values from each day revealed that this observation was only a nonsignificant trend (data not shown). The sedation depth obtained from patients at the PCU was compared to those from patients treated in the hospice or in the setting of SAPV. Patients from the hospice and from the SAPV-setting were pooled for the analysis. For each patient, the median depth of sedation was calculated for every day and the comparison was conducted using the Mann–Whitney U test. Significant differences between both groups were not detected for any day (data not shown).

Table 2. Demographics and diagnoses

Institutions	Entire population (n = 1,124)		Sedated patients (n = 59, 5.25%)		Non-sedated patients (n = 1,065, 94.75%)		p-Value (chi-square test)
	N	Missing data	N	%	N	%	
PCU	340	0	26	7.6	314	92.4	
Hospice	108	18	2	1.8	106	98.2	
SAPV	676	350	31	4.6	645	95.4	
Age (y)	N	Mean	Mean	Range (SD)	Mean	Range (SD)	
PCU	340	70.7	65.6	40–83 (11.4)	71.1	29–94 (12)	0.023
Hospice	90	73.4	82.5	80–85 (3.5)	73.2	45–93 (11.7)	n.s.
SAPV	326	71.8	69.3	37–91 (14)	72.1	22–97 (12.8)	n.s.
PCU							
Gender	N	%	N	%	N	%	n.s.
Male	191	56.2	17	8.9	174	91.1	
Female	149	43.8	9	6.0	140	94.0	
Diagnosis							n.s.
Malignancy	285	83.8	23	8.1	262	91.9	
Other	55	16.2	3	5.5	52	94.5	
Hospice							
Gender	N	%	N	%	N	%	n.s.
Male	48	53.3	1	2.1	47	97.9	
Female	42	46.7	1	2.4	41	97.6	
Diagnosis							n.s.
Malignancy	71	78.9	2	2.8	69	97.2	
Other	19	21.1	0	0.0	19	100	
SAPV							
Gender	N	%	N	%	N	%	n.s.
Male	193	59.2	16	8.3	177	91.7	
Female	133	40.8	15	11.3	118	88.7	
Diagnosis							n.s.
Malignancy	262	80.4	27	10.3	235	89.7	
Other	64	19.6	4	6.3	60	93.8	

Note: PCU, palliative care unit; SAPV, specialized outpatient palliative care service; and n.s., not significant.

Since a major approach of this investigation was the comparison of PS between significantly different institutions, we had to choose a simple and robust scoring system that could be used by health-care professionals as well as by medical amateurs such as the patient's relatives. To consider these preconditions, 3 scoring systems were chosen and each parameter should be scored 3 times per day, accordingly once per shift and once in the morning, in the afternoon, and at night. The depth of sedation was scored by staff members or – in outpatient care – by the palliative care physician according the RASS score (Sessler et al. 2002). The satisfaction with the PS procedure was scored by staff members and by patient's relatives or caregivers from 1 (very good) to 6 (poor). The scoring by health-care professionals and by patient's relatives considers the professional view as well as the emotional view by patient's relatives. Furthermore, it was the goal to compare the degree of satisfaction of the staff and of the patient's relatives with the sedation

procedure. For this analysis, the median degree of satisfaction over the entire sedation period was calculated for each patient and compared between patients treated at the PCU and at the hospice or in SAPV. Comparison was conducted using the independent *t*-test. The degree of satisfaction of the staff was 2.3 (SD: 0.7) at the PCU and 2.3 (SD: 0.8) at the hospice or in the SAPV-setting ($p = 0.86$, Mann–Whitney *U* test). The degree of satisfaction of the patient's relatives was similar with 2.2 (SD: 0.9) at the PCU compared to that from both other settings (hospice/SAPV) in combination with 2.2 (SD: 1.1) ($p = 0.86$, Mann–Whitney *U* test).

Discussion

The rate of PS procedures was significantly higher at the PCU compared to the hospice. Significant differences between PCU and SAPV and hospice and SAPV were not recognized. The reason

Table 3. Indications for palliative sedation

Symptoms	All patients		Institutions					
			Palliative care unit		Hospice		SAPV	
	N	%	N	%	N	%	N	%
Agitation	42	77.8	17	65.4	1	50	24	92.3
Anxiety	31	57.4	16	61.5			15	57.7
Delirium	29	53.7	16	61.5			13	50
Poor QOL	24	44.4	6	23.1	2	100	16	61.5
Dyspnea	22	40.7	12	46.2			10	38.5
Pain	22	40.7	9	34.6			13	50
Nausea/emesis	9	16.7	3	11.5	1	50	5	19.2
Domestic overload	5	9.3	2	7.7			3	11.5
Depressions	5	9.3	2	7.7			3	11.5
Sleep induction	4	7.4	1	3.9	1	50	2	7.7
Seizures	3	5.6	1	3.9			2	7.7
Bleeding	2	3.7	2	7.7				

Notes: Empty box = 0. QOL, quality of life; and SAPV, specialized outpatient palliative care service.

Table 4. Durance of PS and drugs used for PS

Durance	Palliative care unit		Hospice		SAPV	
	N	%	N	%	N	%
	<1 day	8	30.8			4
1–7 days	16	61.5	2	100	16	61.5
>7 days	2	7.7			6	23.1
Drugs						
Midazolam	20	76.9	1	50	23	88.5
Midazolam + Haloperidol	1	3.8	1	50		
Midazolam + Clonidine	1	3.8				
Midazolam + Lorazepam	1	3.8				
Midazolam + Clonidine + Propofol	2	7.7				
Propofol	1	3.8				
Midazolam + Clonidine + Levomepromazine					1	3.8
Levomepromazine					2	7.7

Notes: Empty box = 0. Data from 5 SAPV patients are lacking. PS, palliative sedation; and SAPV, specialized outpatient palliative care service.

for this difference is not clear. One explanation could be that the medical care at the PCU and in the setting of SAPV is realized by specialized palliative care teams, and the patients in the hospice are

often treated by their general practitioner and nursed by volunteers. Another explanation could be that patients can be easily transferred from the hospice to the PCU since both are part of the University Hospital Greifswald.

Since the rate of PS was higher in patients with a spouse, it can be assumed that either the interaction of the patient with her/his spouse or of the spouse with the palliative care team may be important. This was not valid for children since no differences to childless patients were seen. Here, it should be pointed out that the spouse lives commonly in the same household with the patient and adult children living usually in their own household, not having such a close contact to the patient as the spouse has in the same household. This important point should be addressed in future investigations.

The indications for PS in the present investigation are on the whole in accordance with the literature (Arantzamendi et al. 2020; Chater et al. 1998). However, some indications may appear very broad or overlapping with other. This may be owned to the fact that the indications had to be primarily documented within multiple choice options, but one additional free-text field was available. The rationale of this design was to avoid any bias of the documentation on the initiation of PS.

The predominance of midazolam in PS as well as the supplementation with drugs from other classes is common and in accordance with the international literature (Beller et al. 2015; Gamblin et al. 2020; Maltoni et al. 2013, 2012). Major differences in the sedation protocol between PCU and outpatient care were not detected. These results support the hypothesis that a midazolam-based PS can be performed independently from the setting inpatient care or outpatient care.

A quality assessment of PS has been requested by several authors (Alessia et al. 2022; Belar et al. 2020; Brinkkemper et al. 2013). Different scales have been employed for the evaluation of PS; however, standards have not been defined so far. Furthermore, the quality assessment is aggravated by the fact that the main person – the sedated patient – can hardly participate in the evaluation (Brinkkemper et al. 2013; Maltoni et al. 2013).

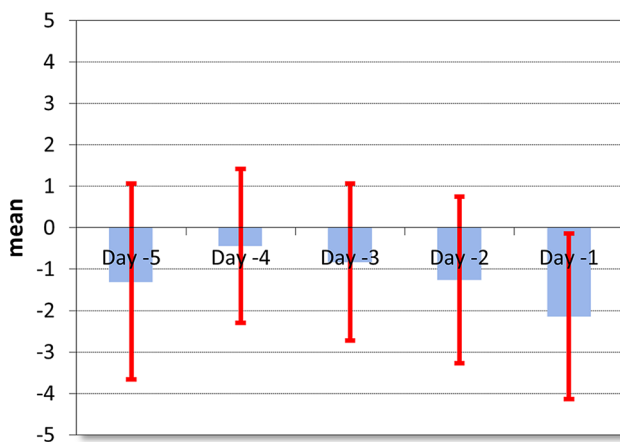
Depth of sedation increased slightly during the last 4 days of the patient; the data did not allow a comparison between PCU and outpatient care. The median degree of satisfaction with the PS was 2 (good) over the entire sedation period, scored by health-care professionals and by patient’s relatives. The variation was broad from 1 (very good) to 6 (poor) in both groups. Significant differences in the degree of satisfaction between inpatient and outpatient care were not detected. Despite the fact that scoring by health-care professional may differ from scoring by patient’s relatives, these results support the evidence that PS can be conducted inpatient and outpatient with comparable satisfaction.

The presented investigation has some limitations and allows a future perspective: The documentation was made by the staff of the PCU for inpatients and by caregivers and relatives for outpatients. A bias due to the professional background and due to psychological factors cannot be excluded here. The RASS has been used for monitoring the depth of sedation in this investigation. This scale has achieved a good rating in a review by Krooupa et al. (2020); however, the authors stated the need for further research to refine the scales. The assessment of consciousness and pain during PS by nonprofessionals may not be objective, and both parameters cannot be always scored correctly with clinical methods. Here, the supplementation with neurophysiological measuring methods can improve the assessment substantially (Six et al. 2021). In addition, this approach would enable a central telemetric monitoring of the patient’s parameters with a quick feedback to the outpatient

Table 5. Depth of sedation according to the RASS and satisfaction of the staff and patient's relatives with sedation procedure

Parameter/score	Day before death (day 0)														
	Day -5			Day -4			Day -3			Day -2			Day -1		
	#1	#2	#3	#1	#2	#3	#1	#2	#3	#1	#2	#3	#1	#2	#3
Depth of sedation															
Minimum (deepest)	-3	-4	-4	-4	-3	-4	-4	-4	-4	-4	-5	-5	-5	-5	-5
Maximum (lightest)	1	3	3	0	1	3	2	1	3	3	3	4	3	4	4
Mean	-1.2	-1.4	-1.3	-2.1	-1.1	-0.1	-0.3	-1.0	-0.6	-1.1	-1.2	-1.4	-1.8	-2.1	-2.3
Median	-1	-1	-1	-2	-1	0	1	-1	0	-2	-1.5	-2	-2	-3	-3
Satisfaction of the treatment team															
Minimum (best)	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Maximum (worst)	4	5	5	3	5	4	5	5	5	6	5	6	5	6	4
Mean	2.6	2.7	2.4	2.2	2.6	2.2	2.4	2.4	2.4	2.3	2.4	2.1	2.3	2.1	1.9
Median	2	2.5	2	2	2	2	2	2	2	2	2	2	2	2	2
Satisfaction of patient's relatives															
Minimum (best)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Maximum (worst)	3	2	3	2	4	4	3	4	5	6	3	5	5	5	5
Mean	2.0	1.7	2.0	1.6	2.0	2.0	2.0	2.2	2.4	2.6	2.0	2.3	2.8	2.0	1.9
Median	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

Notes: Satisfaction was scored from 1 (best) to 6 (worst). Data points available for analysis/patients: RASS, 338/48; satisfaction staff, 293/44; satisfaction relatives, 132/44. RASS, Richmond Agitation Sedation Scale.

**Fig. 2.** Depth of sedation.

treatment team, a possible reduction of bias by the caregivers, and in consequence, a possibly higher comfort for the patients.

The data from the presented investigation support the following theses: a midazolam-based PS is possible in the hospital at the PCU as well as in the outpatient setting when the patient is visited regularly by palliative care physicians. Although the score by both groups shows a wide variation, the median degree of satisfaction was good over the entire period independently from the setting of care. In consequence, an equivalent PS quality can be reached inpatient and outpatient. With the prerequisite of a professional palliative care team, the location for the terminal sedation can be chosen on the base of other medical problems of the patients, on the base of patient's wishes, and on the base of the wishes of the patient's

relatives. An important issue to be considered is the fact that on the PCU, the relatives are relieved from any medical and nursing problems and can concentrate directly on their personal interactions with the patient. Otherwise, some patients and their relatives may prefer dying at home in their familiar environment (Kinoshita *et al.* 2015; Rainsford *et al.* 2016). In both settings, a comparable quality of PS seems possible, this is particularly important for rural areas. Telemetric monitoring of neurophysiological parameters is a possible approach for future improvement of patient's comfort and could be helpful for a more objective evaluation of inpatient and outpatient PS.

Author contributions. BB and AJ contributed equally to this work.

Conflicts of interest. There are no conflicts of interest.

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