Patient-Related Determinants of the Administration of Continuous Palliative Sedation in Hospices and Palliative Care Units: A Prospective, Multicenter, Observational Study

Rogier H.P.D. van Deijck, MD, Jeroen G.J. Hasselaar, PhD, Stans C.A.H.H.V.M. Verhagen, MD, PhD, Kris C.P. Vissers, MD, PhD, and Raymond T.C.M. Koopmans, MD, PhD

De Zorggroep, Region Venlo (EBC) (R.H.P.D.v.D.), Venlo; Department of Anesthesiology, Pain and Palliative Medicine (J.G.J.H., S.C.A.H.H.V.M.V., K.C.P.V.) and Department of Primary and Community Care (R.T.C.M.K.), Centre for Family Medicine, Geriatric Care and Public Health, Radboud University Medical Centre, Nijmegen; and De Waalboog “Joachim en Anna” (R.T.C.M.K.), Centre for Specialized Geriatric Care, Nijmegen, The Netherlands

Abstract

Context. Knowledge of determinants that are associated with the administration of continuous palliative sedation (CPS) helps physicians identify patients who are at risk of developing refractory symptoms, thereby enabling proactive care planning.

Objectives. This study aims to explore which patient-related factors at admission are associated with receiving CPS later in the terminal phase of life.

Methods. A prospective multicenter observational study was performed in six Dutch hospices and three nursing home—based palliative care units. The association between patient-related variables at admission (age, gender, diagnosis, use of opioids or psycholeptics, number of medications, Karnofsky Performance Status scale score, Edmonton Symptom Assessment System distress score, and Glasgow Coma Scale score) and the administration of CPS at the end of life was analyzed.

Results. A total of 467 patients died during the study period, of whom 130 received CPS. In univariate analysis, statistically significant differences were noted between the sedated and nonsedated patients with respect to younger age \( P = 0.009 \), malignancy as a diagnosis \( P = 0.05 \), higher Karnofsky Performance Status score \( P = 0.03 \), the use of opioids \( P < 0.001 \), the use of psycholeptics \( P = 0.003 \), and higher Edmonton Symptom Assessment System distress score \( P = 0.05 \). Multivariate logistic regression analysis showed that only the use of opioids at admission (odds ratio 1.90; 95% confidence interval 1.18–3.05) was significantly associated with the administration of CPS.

Conclusion. Physicians should be aware that patients who use opioids at admission have an increased risk for the administration of CPS at the end of life. In this group of patients, a comprehensive personalized care plan starting at admission is mandatory to try to prevent the development of refractory symptoms. Further research is recommended, to identify other determinants of the administration of CPS and to investigate which early interventions will be effective to prevent the need for CPS in patients at high risk.

Key Words
Determinants, palliative sedation, hospices, nursing home—based palliative care units, refractory symptoms, advanced care planning

Introduction

Patients with a terminal illness can experience severe symptoms during the last phase of their lives.

For some patients, these symptoms become unbearable and refractory, and palliative sedation becomes a last-resort treatment option.\(^1\)\(^2\) Although there is still

Address correspondence to: Rogier H.P.D. van Deijck, MD, De Zorggroep, Region Venlo (EBC), P.O. Box 694, Venlo 5900 AR, The Netherlands. E-mail: rogier.van.deijck@dezorggroep.nl

Accepted for publication: December 23, 2015.

© 2016 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.
a lack of consensus on a definition, palliative sedation has been defined as “the deliberate lowering of a patient’s level of consciousness in the last stages of life” and refers to brief, intermittent, or continuous sedation. Continuous palliative sedation (CPS) aims to reduce proportionally the consciousness of the patient until the moment of death. Although CPS can be administered as a medical intervention at the end of the continuum of palliative care, it must be seen as a last-resort intervention. CPS not only takes away a patient’s suffering, deep CPS also takes away any potential positive and meaningful experiences a patient might have. Besides, research shows that relatives, nurses, and physicians sometimes experience the administration of CPS as a burden.

In palliative care, the early identification, assessment, and treatment of physical, psychosocial, and spiritual problems are important in maintaining quality of life. However, little is known about the early identification of patients at high risk for CPS. Hence, to improve the practice of palliative care and CPS in particular, it is useful to identify patient-related determinants early in the palliative trajectory, associated with the administration of CPS at the end of life. The identification of these determinants could improve advanced care planning and quality of life for high-risk complex patients in a terminal phase. It may help physicians to inform these patients early in the palliative trajectory about the possibility of the administration of CPS in case refractory symptoms occur in the last two weeks of life. In addition, the identification of these determinants helps physicians to become timely aware of and respond to an increased risk of the development of a complexity of symptoms in palliative patients leading to refractory suffering. Early effective interventions in these patients could possibly prevent or decrease the need for CPS.

Therefore, the objective of this study was to identify patient-related determinants of the administration of CPS at admission to a hospice or nursing home-based palliative care unit (PCU). Based on our previously reported review and clinical relevance, we hypothesize that age, gender, diagnosis, use of opioids or psycholeptics, number of medications, functional status, symptom distress, and level of consciousness on admission could be associated with the administration of CPS.

**Methods**

**Setting and Patient Population**

This study involved a prospective observational multicenter study in six hospices and three nursing home PCUs in The Netherlands. Patient admission to these settings is based on an estimated life expectancy of less than three months, according to the referring physician. Inclusion criteria for the study were any new admission during study episode, written informed consent, and an age of 18 years or older.

**Data Collection and Follow-Up**

Data were collected between the first of March 2011 and the first of March 2013 and included a follow-up period of three months. Data collection ended when the patient died, was discharged, or at the end of the study period.

**Measures/Assessments**

The patient’s functional status was evaluated using the Karnofsky Performance Status (KPS) scale. The Dutch-translated version of the KPS is a descriptive ordinal scale that rates the patient’s functional status in 10-point intervals ranging from normal functioning (100) to dead (0). The validity and reliability of the KPS have been shown in patients admitted to a hospice and in cancer patients.

The level of consciousness of the patient was evaluated using the Glasgow Coma Scale (GCS). The GCS has three subscales: eyes, movement, and verbal reactions. The score ranges from 15 (normal consciousness) to 3 (deep comatose). The GCS has good psychometric properties, and its wide use supports the application of the GCS in this study.

To assess symptom severity, the Edmonton Symptom Assessment System (ESAS) was used. This scale consists of nine 100-mm visual analogue scales assessing pain, activity, nausea, depression, anxiety, drowsiness, appetite, sensation of well-being, and shortness of breath. Higher scores reflect greater symptom severity. The symptom distress score is calculated by summing the nine individual symptom scores. The assessment is completed by the patient. In case of a decision-incompetent patient, a family member or nurse completed the ESAS. In this study, a validated Dutch version was used. Although more psychometric research has been advised, the ESAS has been widely adopted in palliative care programs for clinical and research purposes and is a well-recognized and commonly used standard assessment tool for pain and symptom assessment.

The study protocol required completion of the assessments within five days after admission, to prevent contamination of the patient-related factors with clinical interventions from the attending physicians and nurses. Nurses registered the date of admission, gender and age of the patient, KPS, medication use, and GCS on admission. In addition, nurses instructed patients for completing the ESAS. The attending physician recorded the patient’s diagnosis using the International Statistical Classification of Diseases and Related Health Problems 10th Edition. Diagnosis
was defined as “disease(s) which influenced the health status of the patient at admission.” Furthermore, in case the patient died, the physician registered the date of death and whether CPS was administered. Palliative sedation was defined according to the Dutch national guideline, and CPS was defined as “palliative sedation administered until death.”^3 This definition excluded situations in which medication was administered in normal doses to relieve insomnia and/or anxiety, where sedation was an unintended side effect of medication or where palliative sedation was only administered temporarily. The attending physician determined the indication for CPS and the doses, combinations, and duration of the drugs administered. Furthermore, the research protocol did not formalize the discussion with the patient or their representative concerning advanced care planning and CPS. The physician was free in the way he discussed these items, but to get acceptance of the study, obviously, CPS and the possible reasons to start this intervention were discussed at admission.

**Training**

The first author (R. H. P. D. v. D.) provided a half-day training session for the participating nurses and physicians separately. The nurses practiced the assessments using vignettes. Instruction was given on the case report forms and the period of time to complete the assessments. The definitions in the study protocol were explained to the physicians, and patient cases were used to clarify the criteria for CPS.

**Ethical Considerations**

The study followed guidelines for good clinical practice and was conducted after approval of the research ethics committee of the Radboud University Medical Centre (ref 2010/407). Patients or their representatives (in cases of a decision-incompetent patient) were invited to participate via oral and written information. For patients who did not participate, only anonymous demographic data were collected for the purpose of nonresponder analysis.

**Statistical Analysis**

The primary outcome was the administration of CPS. Patients who died were categorized into two groups; those who did and those who did not receive CPS. Patients who were discharged or who were still alive after the follow-up period were excluded from further analyses.

When one or two symptoms were missing from the ESAS, the symptom distress score was calculated via the imputation of the mean score of the known symptoms per patient, so-called ipsative mean imputation. 28 When the ESAS was completed later than five days after admission or when there were more than two missing symptoms, the ESAS symptom distress score was considered missing.

Medication was categorized as opioids (Anatomical Therapeutic Chemical classification N02A); psychaleptics (Anatomical Therapeutic Chemical classification N05); and the total number of drugs with the exclusion of ophthalmic, cutaneous, and rescue medications.

We compared patients who were sedated and who were not on characteristics at admission using independent sampled t-tests and Pearson’s chi-square tests. To assess the independent relationship of the characteristics at admission and the administration of CPS (yes/no), we used a multiple logistic regression model. To take into account the clustering of patients in hospices and PCUs, the location was included in the model.

To handle missing data, we used multiple imputation creating five imputed data sets. All patient characteristics including location were included in the imputation procedure. We combined the results of the multiple logistic regression models across the five data sets.

As a sensitivity analysis, the outcome of the multivariate model without using multiple imputation was also assessed.

The probability of being sedated was calculated in odds ratios (ORs) with 95% CIs. P-values were two-sided, and an alpha <0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 20.0.0 (SPSS, Inc., Chicago, IL).

**Results**

**Patients**

During the study period, of 803 patients admitted to the participating hospices or PCUs, 503 patients gave written informed consent. The included patients (n = 503) did not differ from the excluded patients (n = 300) with regard to gender, age, KPS score (P = 0.20, P = 0.12, P = 0.34, respectively, data not shown) or one of the diagnoses. At the end of the study, four included patients remained alive and 32 included patients had been discharged. A total of 467 patients died and were included for further analysis; 130 of these patients (27.8%) received CPS (Fig. 1). This percentage, with a range of 13.5%−48.1%, was associated with location (Pearson’s chi-square 33.802, df = 8, P < 0.001).

The mean duration from admission until death for the 467 patients was 33.5 days (SD 42.7) with a median duration of 19 days (range 0−305). No significant differences between nonsedated (mean 33.1 days [SD 43.3]) and sedated patients (mean 34.8 days [SD 41.2]) were observed (P = 0.70).
Population and Univariate Analysis

At admission, more than half of the study population consisted of patients aged 76 years and older, having cancer, with a KPS score of 40 or less, and a GCS score of 13 or more. The distribution of men and women was similar. Half of the patients (50.2%) used one or more opioids, and 42.2% of the patients used psycholeptics. The mean number of drugs used was 5.7 (Table 1).

Statistically significant differences were noted between the sedated and nonsedated patients with respect to younger age, malignancy as a diagnosis, higher KPS score, the use of opioids, or the use of psycholeptics (Table 1).

For the ESAS, for two patients more than two symptoms were missing, the ESAS was not completed by 53 patients and 71 patients completed the ESAS later than five days after admission. In univariate analysis, the mean ESAS distress score at admission was significantly higher in the sedated group than in the nonsedated group (Table 1).

Multivariate Analysis

Multivariate logistic regression analysis showed that the use of opioids at admission was significant associated with the administration of CPS (OR 1.90; 95% CI 1.18–3.05; P = 0.008; Table 2). Sensitivity analysis, using a model without multiple imputation, also identified the use of opioids at admission (OR 1.98; 95% CI 1.13–3.46; P = 0.017; data not shown).

Discussion

To our knowledge, this is the first study to prospectively investigate the association between patient-related characteristics at admission and the eventual administration of CPS. We found that only the use of opioids at admission in hospices and nursing home PCUs was independently positively associated with the administration of CPS. No statistically significant independent association was found for gender, age, use of psycholeptics, diagnosis of malignancy, KPS score, GCS score, ESAS symptom distress score, or number of medications on admission.

Results in Relation to Other Studies and Potential Mechanisms

The positive independent association between CPS and the use of opioids at admission could indicate that specific symptoms treated with opioids (such as pain or dyspnea) were more difficult to control in these patients in the palliative trajectory. Caraceni et al. reported that palliative sedation was more frequently indicated in patients with recurrent...
dyspnea in the last seven days of life (OR 4.2; 95% CI 1.9—9.2). Therefore, dyspnea and pain could be the underlying determinants for CPS rather than the use of opioids as such. Additionally, a direct causal relationship between opioid use and CPS could be present because of opioid-induced delirium, which in turn may result in the need for CPS.30—32 Interventions such as opioid rotation and regular screening for and treatment of delirium could reduce the eventually need for CPS in such cases. Patients with opioid use at admission should be informed about the possible side effects of this medication, the need of regular evaluation, and the possible interventions when side effects occur, with CPS as a last-resort intervention. In The Netherlands, the vast majority of the general public accepts the use of palliative sedation at the end of life, although the term palliative sedation is not well known among the general public.33 The finding that many people do not know the term palliative sedation emphasizes the importance to clearly inform patients and relatives about palliative sedation and to verify their beliefs on and expectations of palliative sedation. Information should include that palliative sedation is a last-resort intervention for refractory suffering, that the life expectancy of a patient may not exceed 2 weeks at the moment CPS is started and that CPS has to be distinguished from euthanasia.3

Previous retrospective studies did not focus on an association between the use of psycholeptics and the administration of CPS.13 In this study, the use of psycholeptics at admission showed a marginally significant association with the administration of CPS. Psycholeptics, for example, haloperidol, are usually prescribed for the management of delirium in palliative care.34 Agitated delirium tends to worsen over time and often becomes refractory in the terminal phase leading to palliative sedation.35 For this reason, we assume that the association between the use of psycholeptics at admission and CPS could be a surrogate of an underlying delirium.

When approaching the terminal phase of life, symptoms may exacerbate other symptoms or evolve into a cascade of symptoms; this may lead to a situation in which the patient eventually experiences unbearable and refractory suffering, and an indication for CPS.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Population (n = 467)</th>
<th>Sedated (n = 130)</th>
<th>Not Sedated (n = 337)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55 yrs</td>
<td>23 (4.9)</td>
<td>12 (9.2)</td>
<td>11 (3.3)</td>
<td>0.009*</td>
</tr>
<tr>
<td>55—75 yrs</td>
<td>188 (40.3)</td>
<td>57 (43.8)</td>
<td>131 (38.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;75 yrs</td>
<td>256 (54.8)</td>
<td>61 (46.9)</td>
<td>195 (57.9)</td>
<td></td>
</tr>
<tr>
<td>Gender, number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>224 (48.0)</td>
<td>61 (46.9)</td>
<td>163 (48.4)</td>
<td>0.78*</td>
</tr>
<tr>
<td>Female</td>
<td>243 (52.0)</td>
<td>69 (53.1)</td>
<td>174 (51.6)</td>
<td></td>
</tr>
<tr>
<td>Malignant neoplasms, number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No malignant neoplasms</td>
<td>76 (16.3)</td>
<td>14 (10.8)</td>
<td>62 (18.4)</td>
<td>0.05*</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>391 (85.7)</td>
<td>116 (89.2)</td>
<td>275 (81.6)</td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale (GCS), number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 3—6</td>
<td>18 (4.1)</td>
<td>2 (1.6)</td>
<td>16 (5.1)</td>
<td>0.09*</td>
</tr>
<tr>
<td>Score 7—12</td>
<td>45 (10.2)</td>
<td>9 (7.2)</td>
<td>36 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Score 13—15</td>
<td>378 (85.7)</td>
<td>114 (91.2)</td>
<td>264 (83.5)</td>
<td></td>
</tr>
<tr>
<td>Karnofsky score, number (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.03*</td>
</tr>
<tr>
<td>Score 0—40</td>
<td>368 (79.0)</td>
<td>101 (77.7)</td>
<td>267 (79.5)</td>
<td></td>
</tr>
<tr>
<td>Score 50—70</td>
<td>95 (20.0)</td>
<td>25 (19.2)</td>
<td>68 (20.2)</td>
<td></td>
</tr>
<tr>
<td>Score 80—100</td>
<td>5 (1.1)</td>
<td>4 (3.1)</td>
<td>1 (0.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Opioid use, number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No opioid use</td>
<td>231 (49.8)</td>
<td>46 (35.4)</td>
<td>185 (55.4)</td>
<td></td>
</tr>
<tr>
<td>Opioid use</td>
<td>233 (50.2)</td>
<td>84 (64.6)</td>
<td>149 (44.6)</td>
<td></td>
</tr>
<tr>
<td>Psycholeptics use, number (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.003**</td>
</tr>
<tr>
<td>No psycholeptics use</td>
<td>268 (57.8)</td>
<td>61 (46.9)</td>
<td>207 (62.0)</td>
<td></td>
</tr>
<tr>
<td>Psycholeptics use</td>
<td>196 (42.2)</td>
<td>69 (53.1)</td>
<td>127 (38.0)</td>
<td></td>
</tr>
<tr>
<td>Number of medications, mean (SD)</td>
<td>5.7 (3.5)</td>
<td>6.1 (3.2)</td>
<td>5.5 (3.6)</td>
<td>0.06*</td>
</tr>
<tr>
<td>ESAS distress score 9, mean (SD)</td>
<td>37.5 (15.4)</td>
<td>40.1 (16.2)</td>
<td>36.4 (15.0)</td>
<td>0.05*</td>
</tr>
</tbody>
</table>

ESAS = Edmonton Symptom Assessment System.

Data were missing for the Karnofsky score in one patient, on opioids, psycholeptics, and number of medications for three patients.

For ESAS, 126 patients were excluded in univariate analysis: six symptoms were missing for one patient, eight symptoms for one patient, and all symptoms for 53 patients. Seventy-one patients completed the scale later than five days after admission. Ipsative mean imputation was used in 20 patients: one symptom was missing for 19 patients, two symptoms for one patient. There was no significant difference in the distribution of missing data between the sedated and nonsedated groups.

Data on GCS were missing for 26 patients.

Values in bold are significant.

Chi-square test.

Student t-test.

Data were missing for the Karnofsky score in one patient, on opioids, psycholeptics, and number of medications for three patients.

For ESAS, 126 patients were excluded in univariate analysis: six symptoms were missing for one patient, eight symptoms for one patient, and all symptoms for 53 patients. Seventy-one patients completed the scale later than five days after admission. Ipsative mean imputation was used in 20 patients: one symptom was missing for 19 patients, two symptoms for one patient. There was no significant difference in the distribution of missing data between the sedated and nonsedated groups.

Data on GCS were missing for 26 patients.

Values in bold are significant.

Chi-square test.

Student t-test.

For ESAS, 126 patients were excluded in univariate analysis: six symptoms were missing for one patient, eight symptoms for one patient, and all symptoms for 53 patients. Seventy-one patients completed the scale later than five days after admission. Ipsative mean imputation was used in 20 patients: one symptom was missing for 19 patients, two symptoms for one patient. There was no significant difference in the distribution of missing data between the sedated and nonsedated groups.
A Multiple Logistic Regression: Determinants of Continuous Palliative Sedation, Measured at Admission to a Hospice or a Palliative Care Unit (n = 467)

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Direction (Reference)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male (female)</td>
<td>0.97</td>
<td>0.62–1.52</td>
<td>0.91</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>Present (not present)</td>
<td>1.42</td>
<td>0.68–2.93</td>
<td>0.35</td>
</tr>
<tr>
<td>Opioid use</td>
<td>Present (not present)</td>
<td>1.90</td>
<td>1.18–3.05</td>
<td>0.008</td>
</tr>
<tr>
<td>Psycholeptics use</td>
<td>Present (not present)</td>
<td>1.57</td>
<td>1.00–2.49</td>
<td>0.05</td>
</tr>
<tr>
<td>Age</td>
<td>Older</td>
<td>0.98</td>
<td>0.96–1.00</td>
<td>0.12</td>
</tr>
<tr>
<td>Karnofsky score</td>
<td>Higher</td>
<td>1.06</td>
<td>0.86–1.29</td>
<td>0.39</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>Higher</td>
<td>1.10</td>
<td>0.96–1.27</td>
<td>0.16</td>
</tr>
<tr>
<td>Number of medications</td>
<td>Higher</td>
<td>1.02</td>
<td>0.95–1.09</td>
<td>0.60</td>
</tr>
<tr>
<td>ESAS</td>
<td>Higher</td>
<td>1.01</td>
<td>0.99–1.03</td>
<td>0.24</td>
</tr>
</tbody>
</table>

ESAS = Edmonton Symptom Assessment System.
Nagelkerke R square 0.19.
Values in bold are significant.
*For psycholeptics, the CI to three decimal places was 0.996 to 2.489, with a P-value of 0.052. For age, the CI to three decimal places was 0.964 to 1.004, with a P-value of 0.115.
Continuous variable.

Therefore, our hypothesis was that a higher symptom distress score at admission would be a risk factor. However, the results of this study did not support this hypothesis. It is possible that specific symptoms such as pain or agitation, rather than the aggregated score, could have influenced the chance of CPS. The sample size of our population, although considerable for palliative care research, did not allow for a subanalysis of individual symptoms or clusters, that is, the use of opioids and the symptoms pain and dyspnea.

In contrast to previous retrospective studies, the multivariate analysis in our prospective study did not confirm an association between male or younger age patients and the administration of CPS. However, our study population differed from the retrospective studies by including only a small number of young adults and being restricted to a hospice and nursing home PCU setting.

Literature reports an association between the presence of cancer and the administration of CPS. None of these retrospective studies included symptoms or symptom distress scores in their multivariate model. In the univariate analysis, our study demonstrated significant differences between the sedated and nonsedated patients regarding the diagnosis of malignancy; however, the multivariate analysis did not confirm this association.

Although we focused on patient-related factors, this study showed also that location is associated with the administration of CPS. The umbrella term location makes it difficult to identify the specific underlying factors of this term. A review on determinants of CPS from the literature showed that the following non–patient-related factors were associated with the administration of CPS: very or extremely nonreligious physicians, physicians working in “other hospital” specialties, physicians in favor of assisted death, and Dutch-speaking community setting in Belgium. Besides, other characteristics of health care providers and characteristics of location, that is, what is allowed in a location based on the religious affiliation, could also be an explanatory factor that results in differences in the administration of CPS between locations. Furthermore, the “how” of determining intolerability of suffering and refractoriness is not established in guidelines. This can result in subjectivity in determining the refractoriness of symptoms and therefore in variation of the eventually administration of CPS. Our study was not intended to find location-dependent variables, but our results underline the need to perform such a study in the future.

Strengths and Limitations

A strength of this study was its prospective multicenter design, the clear operational definition of CPS and the use of validated, clinically relevant assessments at a well-defined time point. Additionally, the large number of sedated patients made it possible to look at the independent relationship of multiple characteristics at admission and the administration of CPS in the terminal phase of life.

Nevertheless, some limitations of this study warrant attention. First, an important limitation of this study is the number of protocol violations and missing components of some patients’ ESAS, which influenced the power of the study and therefore its validity. However, multivariate models with and without multiple imputation were used to control for understating uncertainty. These models showed a similar association between the administration of CPS at the end and the use of opioids at admission.

Second, assessments were performed at admission to identify patients who were at risk of developing refractory symptoms at the end of the palliative trajectory. However, we could not determine whether the associations found in this study were time sensitive or not.

Third, 503 of 803 patients (62.6%) participated in our study. Although the 503 patients were a representative sample regarding gender, age, KPS, and diagnosis of the total population, nonresponder bias cannot be excluded.

Fourth, the reported variability in the administration of CPS in our study could reflect a different understanding of CPS among the participating physicians and nurses. However, we did all efforts to
minimize this, by providing a training where the definitions in the study protocol were explained and patients’ cases were used to clarify the criteria for CPS. Furthermore, previous reported research on palliative sedation showed that almost all physicians reported that they knew about the Dutch national guideline and mostly rated their level of knowledge about the contents of the guideline as good to excellent.42

Finally, this study was performed in hospices and nursing home PCUs in The Netherlands. Most patients were aged 76 years and older with a low Karnofsky index, reflecting a relatively low functional status. The findings in this study may not be generalizable to other populations, care settings, and countries.

Conclusion

This study showed that the use of opioids at admission to a hospice or PCU was independently positively associated with the chance of the administration of CPS. In patients with this characteristic, physicians should be aware of the higher risk of developing refractory symptoms leading to CPS in the terminal phase of life, and a comprehensive care plan, including end-of-life interventions that meet the patient’s goals, values, needs, and preferences, should be developed early in the palliative trajectory. Besides, physicians should inform these patients early in the palliative trajectory about the possibility of the administration of CPS in case refractory symptoms occur in the last two weeks of life. This study was not performed to unravel the specific underlying symptoms or mechanism that increases the chance of patients with opioid usage to develop refractory symptoms in the end stage of life. Further studies will be necessary to find such mechanisms. Furthermore, such research should find other determinants of the administration of CPS, involving different settings and populations, and finally examine if interventions based on such knowledge will be effective to prevent the development of refractory symptoms in the terminal stage of life of these high-risk patients, and eventually the need for CPS.

Disclosures and Acknowledgments

This study was funded by the care organization “De Zorggroep.” This organization employed the primary investigator throughout the study period. The organization was not involved in the design of the study, data collection, data processing, article preparation, or the decision to publish. The authors declare no conflicts of interest.

The authors thank Hans Bor, BSc (Mathematics), Department of Primary and Community Care: Centre for Family Medicine, Geriatric Care and Public Health, Radboud University Medical Centre, who helped them with the statistical analysis. The authors also thank the physicians and nurses who cared for the patients at the participating institutions. Finally, the authors thank all the patients who agreed to participate in the study.

References


