

Retrospective Observational Study about Patient's Profile who Received Palliative Sedation Therapy at the Palliative Care Unit in a Brazilian Cancer Hospital

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Estudo Observacional Retrospectivo sobre o Perfil de pacientes que Receberam Terapia de Sedação Paliativa em Unidade de Cuidados Paliativos de Hospital de Câncer no Brasil

Estudio Observacional Retrospectivo sobre el Perfil de Pacientes que Recibieron Terapia de Sedación Paliativa en Unidad de Cuidados Paliativos de Hospital de Câncer en Brasil

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Abstract

Introduction: The World Health Organization estimates that 27 million new cases of cancer will occur until 2030 around the world. In 2017, 597.000 new cases were expected to occur in Brazil with 70% of lethality rate. Palliative Care comprises end of life care, and physical symptom control is one of the aims of its actions. Eventually, the symptoms can be refractory. For such cases, the Palliative Sedation Therapy (PST) is an option, that is the use of drugs to reduce or abolish patient's consciousness to relieve suffering. Studies have demonstrated that using suitable techniques does not shorten patient's life. **Objective:** To identify patient's profile that received PST at the end of life. **Method:** Cross-sectional observational study collecting data from patients records who died at a palliative care unit of a cancer hospital in 2015. Data was collected regarding demographics, proportion of patients who received PST, what were the more frequent symptoms, the more used drugs, the average dose used, if any discussion with the Family or the team occurred, the length of PST in days, and the survivorship until death. **Results:** In 2015 there were 919 deaths, 198 (21.5%) received PST, 55.1% were female, the average age was 55 years-old. The most frequent symptoms at the time of indication were dyspnoea (64.1%), pain (36.3%), and other symptoms (30.3%). The most frequent used drug was midazolam (98%) and the most frequent modality used was continuous sedation (75.8%). **Key words:** Deep Sedation; Palliative Care; Neoplasms; Delirium; Observational Study.

Resumo

Introdução: A Organização Mundial da Saúde estima que até 2030 ocorrerão 27 milhões de novos casos de câncer no mundo. Em 2017, esperava-se em torno de 597 mil novos casos no Brasil com letalidade de 70%. Os cuidados paliativos incluem os cuidados de final de vida, e o controle dos sintomas físicos é um dos focos de suas ações. Eventualmente, os sintomas podem se tornar refratários. Para esses casos, existe a opção da terapia de sedação paliativa (TSP), que é o uso de fármacos para reduzir ou abolir a consciência do paciente com o objetivo de aliviar o sofrimento. Estudos demonstram que o uso da técnica adequada do procedimento não encurta a vida do paciente. **Objetivo:** Identificar o perfil dos pacientes que receberam TSP no final da vida. **Método:** Estudo observacional retrospectivo com coleta de dados em prontuário dos pacientes falecidos na unidade de cuidados paliativos de um hospital de câncer no ano de 2015. Foram coletados dados demográficos, proporção de pacientes que necessitaram de TSP, indicações mais frequentes, drogas mais utilizadas, doses médias usadas, se discussões com família e/ou equipe foram realizadas, duração da TSP em dias e sobrevida do paciente até o óbito. **Resultados:** Em 2015, ocorreram 919 óbitos; 198 (21,5%) receberam TSP; 55,1% do sexo feminino; média de idade de 55 anos. Os sintomas mais frequentes no momento da indicação foram dispnéia (64,1%), dor (36,3%) e outros sintomas (30,3%). A droga mais utilizada foi o midazolam (98%) e a modalidade mais utilizada foi de sedação contínua (75,8%).

Palavras-chave: Sedação Profunda; Cuidados Paliativos; Neoplasias; Delírio; Estudo Observacional.

Resumen

Introducción: La Organización Mundial de la Salud estima que hasta 2030 deberán ocurrir 27 millones de nuevos casos de cáncer en el mundo. En 2017, se esperaba alrededor de 597 mil nuevos casos en Brasil, con 70% de letalidad. Los Cuidados Paliativos incluyen los cuidados de fin de vida y el control de los síntomas es uno de los focos de sus acciones. Eventualmente, los síntomas pueden se tornar refractarios. Para esos casos, existe la opción de la Terapia de Sedación Paliativa (TSP), que es el uso de fármacos para reducir o abolir la conciencia del paciente con el objetivo de aliviar el sufrimiento. Los estudios demuestran que el uso de la técnica adecuada del procedimiento no acorta la vida del paciente. **Objetivo:** Identificar el perfil de los pacientes que recibieron la TSP al final de la vida. **Método:** Estudio observacional retrospectivo con recolección de datos en prontuario de los pacientes fallecidos en la unidad de cuidados paliativos de un hospital de cáncer en el año 2015. Se recolectaron datos demográficos, proporción de pacientes que necesitaron TSP, indicaciones más frecuentes, drogas más utilizadas, dosis medias, se utilizaron las discusiones con la familia y / o el equipo, la duración de la TSP en días y la supervivencia del paciente hasta la muerte. **Resultados:** En 2015 ocurrieron 919 muertes, 198 (21,5%) recibieron TSP, 55,1% del sexo femenino, promedio de edad de 55 años. Los síntomas más frecuentes en el momento de la indicación fueron disnea (64,1%), dolor (36,3%) y otros síntomas (30,3%). La droga más utilizada fue el midazolam (98%) y la modalidad más utilizada fue sedación continua (75,8%).

Palabras clave: Sedación Profunda; Cuidados Paliativos; Neoplasias; Delirio; Estudio Observacional.

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INTRODUCTION

According to the World Health Organization, Palliative Care is an approach that promotes quality of life to patients and their family, who face diseases that threaten the continuity of the life through prevention and relief of the suffering. Requires the early identification, evaluation and treatment of the pain and other physical, psychosocial and spiritual problems¹.

Cancer is the second world cause of deaths and in 2015, it was responsible for 8.8 million deaths in the world. In low and medium income countries, the disease generally presents itself in advanced staging, which, then, makes the patients eligible for palliative care.

These are the principles that the team of palliative care must follow: provide relief from pain and other distressing symptoms; affirm life and regard death as a normal process of life, intend neither to hasten or postpone death, integrate the psychological and spiritual aspects of the patient care, offer a support system to help patients to live as actively as possible until death, offer a supportive system to help the family to cope during the patient's illness and in their own bereavement, multiprofessional approach to address the needs of the patients and their families, including follow up during mourning, enhance the quality of life and positively influence the course of the disease, palliative care is applicable as early as possible, in conjunction with other therapies intended to prolong life as chemotherapy and radiotherapy and include all the required investigations to better understand and manage distressing clinical complications.

Palliative care is best known in oncology, but can also be applied in other circumstances of diseases without possibility of cure¹. Seventy percent of the persons diagnosed with cancer in the world will die as a consequence of the disease that causes anguish, pain, distress physically, psychosocially and spiritually. To reach this goal, it is necessary to meet four essential steps³: good control of the pain and other symptoms; good communication; psycho-social support, team work.

It is common the prevalence of distressing symptoms in the end of the life, among them, pain, dyspnea, *delirium*, nausea and vomits, intestinal constipation and respiratory secretions that, if not well controlled, may lead to intense distress⁴. If therapeutic options fail, it may be necessary to apply palliative sedation therapy (PST)⁵⁻⁷. The term was proposed by Morita, Tsuneto and Shima⁸ after completing a systematic review about the use of common terms of the procedure at the time, although more recently it has been used the term "continuous deep sedation palliative therapy until death" to refer to continuous deep sedation therapy⁹.

Ventafrida et al.¹⁰ described palliative sedation for the first time in 1990 and, ever since, this concept has raised controversies and diverse perspectives of understanding, mainly because of ethical aspects, since the intent of whom indicates and practices sedation is subjective and could mask the intention to abbreviate life. Furthermore, the intention is one of the points that distinguishes PST from euthanasia⁴. Palliative sedation is defined as introduction of medication to reduce the level of awareness of a patient with advanced disease or in palliative care with its consent or its family with the objective of bringing relief of refractory symptoms that did not respond to the therapeutic adopted⁷. Refractory symptom is defined as the symptom that cannot be properly controlled regardless of intense efforts to identify a therapy that does not compromise the consciousness and the clinical doctor must be aware of the fact that invasive or noninvasive interventions are considered refractory, being unable to promote proper relief, either associated to acute or intolerable chronic morbidity and are unlikely to produce relief within an acceptable time¹¹. The national literature is scarce in articles and studies about this theme, which justifies the current research. The objectives were to analyze the prevalence of PST in patients attended in a cancer hospital palliative care unit and how this sedation occurred with indication, duration, modality, drugs of choice and doses.

METHOD

It is a retrospective observational study. It were evaluated 919 patients' charts that died in a palliative care unit in 2015. As it were utilized data of all the patients who died in a Brazilian cancer palliative care unit, this sample was characterized as non-probability by convenience. To be eligible to the study, the following inclusion criteria were complied with: patients who died in 2015, over 18 years old, of both genders who received any type of sedation. Exclusion criteria: death without sedation, lack of notes about the subject. The charts that complied with the criteria mentioned were selected and the information registered through a data collection form. This work complied with Resolution 466 dated December 12, 2012.

The following information were collected: demographic data, primary location of the tumor, metastatic site, gender, age, education, number of patients that used PST in relation to the total number of deaths in 2015, most frequent indications, most utilized drugs, effective average doses to produce sedation, duration of the sedation, survival of the patient up to death, whether there was a meeting with the team or the family to decide for the procedure. The Institutional Review Board of "Hospital

de Câncer de Barretos” approved the study, report number 1.684/214, CAAE 57873716.2.0000.5437.

The descriptive analyzes of the variables collected were tabulated. Tables with absolute and relative values were utilized for the qualitative variables. For the quantitative variables, statistic measures as mean, standard deviation (SD), minimum, maximum values and quartiles were used.

It was calculated the time since the sedation until the death of the patient to evaluate the survival, whose event of interest was death. Kaplan-Meier curves and Log-rank tests were utilized in this phase.

The statistical analyzes were performed with the software SPSS version 21, level of significance of 5%.

RESULTS

This sample was formed by 919 charts of patients who died at the palliative care unit in 2015. Of this total, 198 (21.5%) received PST, either superficial or deep, continuous or intermittent, therefore, eligible for the study. Of the patients who received PST, 109 (55.1%) were females, average age of 55 years old when initiated the follow up with the palliative care team (SD = 14; 19-85), 124 (62.6%), living in the state of São Paulo and 88% had cancer in clinical staging III or IV when admitted to the palliative care unit. The other clinical or sociodemographic data can be seen in Table 1. The tumors of the digestive system were the most often encountered and the oncologic diagnostic profile is seen in Figure 1.

The most frequent symptom in the moment of indication of PST was dyspnea, followed by pain and other symptoms. Figure 2 shows the description of all the indications and Figure 3 details each symptom classified in the category “others”.

The modality of continuous sedation was the most frequent, being utilized in 150 patients (75.8%). The sedation lasted until death in 188 patients (95.4%) and was suspended before death in nine patients. The motives for the suspension were medical decision in five patients, requested by the family for two patients and for two patients it was not possible to find the reason.

Midazolam was the drug of choice in 194 patients (98%) of the cases, followed by phenobarbital in three cases (1.5%), and levomepromazin in one case (0.5%). The initial dose in mg/24 hours of midazolam requested was 23.06 mg (SD=22.94; 2.00-200.0) and the average dose after the titration when sedation was reached was 32.41 mg (SD = 28.47; 2.00-185.00). The duration of the sedation until death in the continuous modality was 2.77 days (SD=0.36; 2.07-3.47) and in the modality of intermittent sedation was 8.18 days (SD=1.5; 5.3-11.1).

Table 1. Clinical and sociodemographic data

	N	%
Total deaths in 2015	919	100,0
Sedated	198/919	21.5
Continuous palliative sedation therapy	150/198	75.8
Intermittent palliative sedation therapy	48/198	24.2
Remained sedated until death	188/198	95.0
Female	109/198	55.0
Age average at admission at Palliative Care Unit (years)	54	-
Clinical Staging		
Stage I	7	3.5
Stage II	13	6.5
Stage III	36	18.2
Stage IV	111	56.0

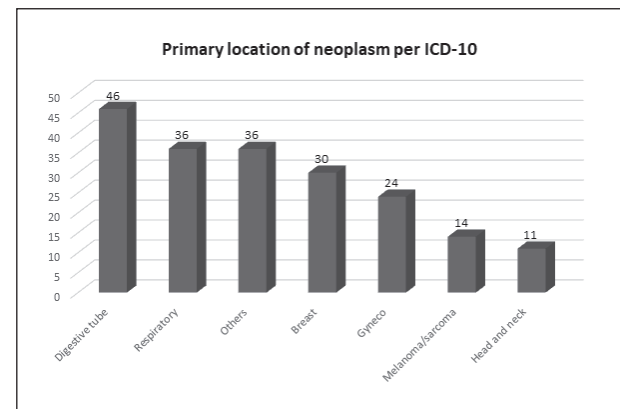


Figure 1. Distribution of most frequent diagnosis

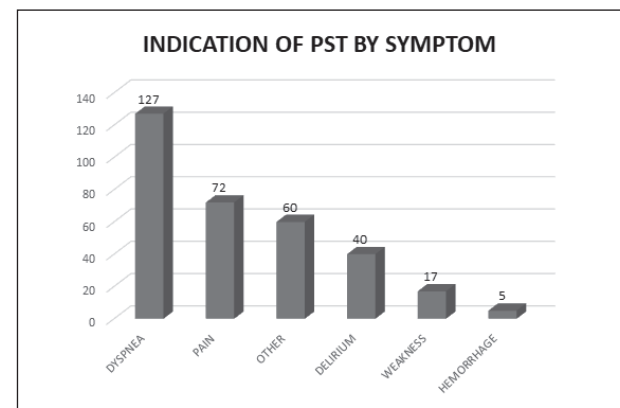


Figure 2. Distribution of most frequent indications

The survival of patients submitted to intermittent PST was bigger than of the patients submitted to continuous PST (Figure 3), the average and the median are shown in Table 2.

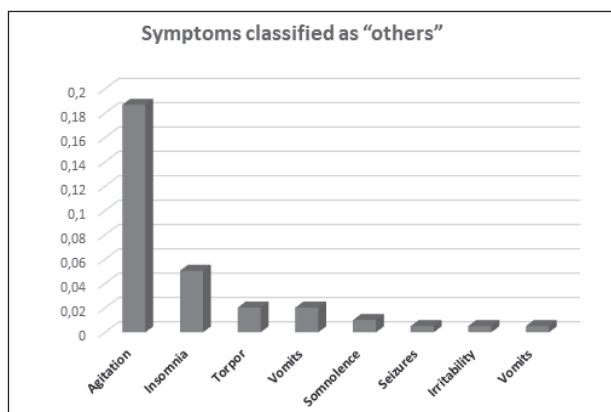


Figure 3. Symptoms classified as "others"

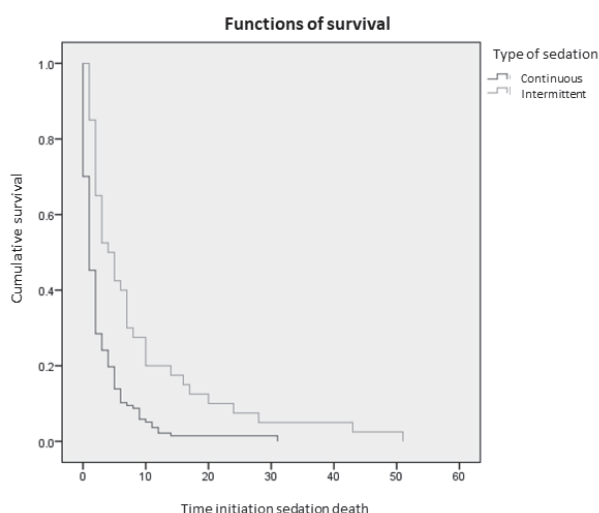


Figure 4. Comparison of the survival curves between intermittent and continuous sedation

Table 2. Survival after the beginning of sedation (days)

Types of Sedation	Survival	
	Mean	Median
Continuous	2.77	1.00
Intermittent	8.18	5.00

The decision making with the family occurred and was registered in the chart 140 times (71.1%) and with the team, it happened 13 times (6.6%).

DISCUSSION

Some patients, in the last weeks of life, experienced suffering considered unendurable, when the procedures known as best clinical practice were used to the limit and for whom PST begins to be a robust therapeutic

decision⁵. Regardless of being adopted since the decade of 1990 in the XX century¹⁰, it is a procedure that is still controversial due to the ethical perspective through which PST is approached, because until recently it was believed that it anticipated the death of the patient¹² and, while the conscience of the patient is abolished, the patient was placed in a euthanasia-like condition, then called slow euthanasia¹³. Despite this, it continues being widely practiced. In 2015, the library Cochrane published a systematic review that obtained 14 valid studies for analysis according to the inclusion criteria defined for this review. However, there were not enough homogeneity to produce a meta-analysis, the bias analyzes were poor and it was not possible to produce a consistent evidence¹⁴. The most recent recommendations were based in consensus about what is more practiced^{12,15}.

The publications about the theme in Latin America are rare, which motivated this research. According to the data of the world literature, the average prevalence of PST is 27%, ranging from 12% to 67%¹⁴. Our data showed a prevalence of 21.5% close to the global average, but somewhat below this average. There is no evidence that recommend or standardize a specific value as reference for the prevalence of PST.

In this study, the practice of continuous PST was more prevalent, it was applied in 105 patients, corresponding to 75.8% of the patients. However, it was not foreseen the registry whether the modality chosen was superficial or deep, yet the literature is abundant about continuous and deep sedation¹⁶⁻¹⁹ and scarce in relation to superficial and intermittent, which leads to ambiguous interpretations about the intent of the procedure at the moment of its indication¹⁸.

Of the 14 studies elected for Cochrane review, ten (71.4%) reported the indication to start PST. Of these, in six studies, *delirium* was the first indication, having appeared in seven studies. Dyspnea, though having appeared as first indication in only two, were present in nine studies as one of the main indications for sedation. Agitation was also described as motive to indicate PST. However, agitation can be one of the symptoms of *delirium* and, for this, the frequency of *delirium* may be underestimated because of the variation with which it is described. In our study, dyspnea was the first indication in 64.1% of the times, followed by pain (36.4%) of the indications and others in third place with 30.3% of these indications. These data differ from the encountered in an Austrian study where the most frequent symptom was *delirium* (51%), followed by existential distress (32%) and pain (20%)²⁰. It also differed from other study where the motives to sedate declared by an expert caretaker in palliative care were dyspnea (56%), *delirium* (53.9%)

and pain (50%) in a multiple choice questionnaire¹⁶ and also coincided with a German study that found terminal agitation (56%), dyspnea (39%) and pain (32%)²¹. It is believed that the form how the information is recorded in hospital documents and the interpretation of the investigators responsible for the collection of data, may have introduced a bias in the result in which the option “others” appears more frequently as indication of PST. This fact corroborates the hypothesis of Morita, who affirms that the lack of consensus about the definition related to palliative care promote conflicting results and conclusions and proposes a standard to conduct researches about PST⁹. Still elaborating about the motive “others”, comprehending other symptoms, among them, agitation (18.7%), insomnia (5.1%), irritability, somnolence and torpor (0.5% for each) may have been manifestations of *delirium* which eventually were poorly interpreted, contributing for a bias of the results. This event brings the hypothesis that may be *delirium* has been a bigger prevalence and was the most frequent motive for the indication of PST in the sample investigated.

In relation to the average dose utilized to start the process of PST, the dose was 23.06 mg and the average dose to obtain the sedation was 32.41 mg in 24 hours. According to the Cochrane review, only three studies recorded the dose of midazolam necessary to obtain sedation and the average was 37.06 mg in 24 hours. Midazolam has been chosen as the preferable drug based in the consensus and because of its pharmacologic properties of fast initiation and short half-life, which allows a rapid titration and superficialization of the level of consciousness^{12,15}.

According to the data of this study, PST lasted 2.77 days in average in the modality continuous and 8.18 days in the modality intermittent. As parameter of comparison, it were used the data of the Cochrane review, which identified eight studies that brought this data in the results. It was calculated the means obtained in the study and the average duration was 1.86 days. In regard to survival of the same review, it was of 20.5 days in sedated patients against 20.5 days of non-sedated patients. Though the data are not uniform and the authors of the review have not calculated the mean because of the lack of homogeneity among the studies, this mean was calculated according to the available data. In our study, as there was no control group, the survival of the patients was not calculated.

The results presented are considered consistent, but some fragilities were observed that bring some risks of bias for the data that should be considered in their interpretation. One of them was the episode of not registering the characteristic of the sedations according to the depth in order to obtain national data about this

subject. This can be explained by the lack of a description in the chart or the use of scales of evaluation of sedation. Therefore, it was not possible to affirm what was the prevalence of superficial compared to deep sedation. It is important to emphasize this detail, because the world literature is abundant in productions about continuous deep PST or continuous deep sedation until death, which has been challenged as a concept of euthanasia in that continent^{16-19,22}. Another fragility is the fact that it was necessary to collect qualitative data as they were registered in the chart. This may have affected the interpretation of each investigator in the moment of registering the data in the data collecting form, which impacted specially two aspects analyzed in this study: (I) the indications to start PST; and (II), registering the discussion with the team and the family in the process of initiating PST. In regard to the indications, they were not described objectively, which limited the collection of data about the symptoms present in the moment of the indication of PST. At last, another limitation of this work is the fact that it is retrospective, which restrained the verification of the data of the content that was available in the patients' records and how the contents were registered, which brings the heterogeneity of the information and hinders a more consistent analysis.

CONCLUSION

The prevalence of PST in a Palliative Care Unit of a Brazilian Cancer Hospital was of 21.5%. The drug more often used was midazolam and the final average dose in 24 hours to reach a satisfactory sedation was 32.41 mg. The most frequent indication was dyspnea, pain and other motives. The modality of continuous deep sedation and its average duration was 2.77 days. However, a bias may have been present in the collection of data either in the interpretation or form of registration.

More prospective studies are necessary in different regions and services throughout the country to evaluate whether the parameters analyzed in this study have been impacted somehow by any local reality fact.

It is necessary to stimulate palliative care teams to register clearly and comprehensively the aspects related to the process of indication and execution of PST, such as: indications (motive) for PST, what is the modality (whether continuous or intermittent, superficial or deep), discussion with the team and if it means discomfort to any member of the team and discussion with the family. Equally important is to record which is the drug of choice, the initial dose and the effective dose to produce the desired level of sedation, time of sedation and survival of the patients.

CONTRIBUTIONS

Renata Batista dos Santos contributed substantially for the conception, planning and collection of data and wording. Camila Moreira Gomes, Carla Baioni Bonadio, Paula de Souza Ferreira and Raquel Barducci Bertequini contributed for the collection of data. Luís Fernando Rodrigues contributed substantially for the conception, planning, analysis and interpretation of data, wording and critical review. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There are no conflict of interests to declare.

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