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ORIGINAL ARTICLE

Palliative sedation in pediatric patients with advanced cancer in palliative care

Sedación paliativa en pacientes pediátricos con cáncer avanzado en cuidado paliativo

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What do we know about the subject matter of this study?

In the adult population, palliative sedation (PS) is a common practice in palliative care. To date, publications on PS are based on adult protocols, with few reports in pediatric patients, and even fewer in Latin America.

What does this study contribute to what is already known?

This study describes a series of pediatric cancer patients in palliative care who received PS. The clinical characteristics are described with dyspnea as the most frequent refractory symptom, and midazolam as the most indicated drug.

Abstract

Palliative care (PC) plays a fundamental role in the pediatric population suffering from cancer, with few publications on the palliative sedation (PS) procedure in this group of patients. **Objective:** to describe the characteristics of patients treated in the PC Unit of the *Hospital de Niños Dr. Roberto del Río*, with an advanced stage oncological diagnosis who received PS. **Patients and Method**: Retrospective descriptive study. Clinical histories of children and adolescents with advanced cancer who received Palliative Sedation (PS) between 2003 and 2021 were reviewed. Variables were characterized in relation to patients and PS practice. **Results:** 204 patients with cancer were included between 2003 and 2021; 22.5% received PS (46/204). We reviewed 36 medical records, the mean age was 8 years 7 months, 56% were male, and 45% with solid tumors. The most frequent refractory symptom was dyspnea (50%). 97 % received midazolam in continuous infusion. The time between the start of PS and death was greater than 72 hours in 44% of the patients. 72% of the sedated patients died hospitalized in low complexity units. **Conclusions:** PS in children and adolescents in PC due to advanced cancer is a therapeutic tool, for occasional use, indicated for refractory symptoms, allowing optimizing the management of patients at the end-of-life stage. More multicenter studies are required to provide guidance that includes patients with non-oncological pathology.

Keywords:
Palliative Care Nursing;
Palliative Care;
Pediatrics;
Cancer;
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Introduction

Childhood cancer is one of the main causes of death in children and adolescents worldwide, and in Chile, it represents the second cause in the population aged between 5 and 15 years[1]. Despite advances in its treatment, a percentage of patients will die due to the progression of this disease, which is generally associated with an experience of suffering in the last days of life. In this context, the role played by Palliative Care (PC) teams working in childhood cancer units in our country's hospital network is essential to provide symptom relief and support for children and adolescents and their families[2].

The World Health Organization (WHO) recognizes PC as an ethical responsibility of health systems and defines it as "the active care of the body, mind, and spirit of the child with a life-threatening and/or life-limiting illness"[3]. This care should be incorporated throughout the disease process of oncology patients, especially at the end of life, since, as the American Academy of Pediatrics points out, "it is not always possible to eliminate symptoms, but it is always possible to alleviate suffering"[4].

Palliative sedation (PS) is a tool available to PC teams for the management of end-of-life patients. It is defined as the intentional administration of drugs with sedative effect, in doses and combinations required to reduce the level of consciousness of a patient with advanced disease, as much as necessary, to adequately relieve one or more refractory symptoms[5]. In this context, PS is a medical indication, but it should be agreed with the parents or caregivers and the patient when possible[6].

PS has precise indications, which are better known and studied in the adult population[7]. Few publications in Latin America describe its use against refractory symptoms at the end of life in children and adolescents and there are no publications to date in our country[8,9]. In Spain[10] and Japan[11], retrospective studies were carried out in children who received PS, representing the first pediatric studies in their respective countries, both based on adult guidelines, with a follow-up of 5 and 9 years, respectively, describing the usefulness of PS in the management of complex end-of-life symptoms.

PC is currently considered an essential part of the treatment for childhood cancer, and providing it is a standard of quality[12]. However, the experience in PC in this age group is based on the recommendations of expert groups for adult patients which, associated with the lack of experience of PC teams that care for children and adolescents, may lead to underuse of this resource in the pediatric population[13,14].

The objective of this study was to describe the characteristics of patients with advanced-stage cancer, who received PS, treated at the Palliative Care Unit of the *Hospital de Niños Dr. Roberto del Río*, and to describe the practice of PS in this group of patients.

Patients and Method

Retrospective descriptive study which reviewed the medical records of children and adolescents with a diagnosis of advanced childhood cancer treated at the PC and pain relief unit of the *Hospital de Niños Dr. Roberto del Rio*, from January 2003 to December 2021.

All patients whose clinical records described having received PS as part of the management of a refractory symptom were considered eligible. As a refractory symptom were considered those symptoms that could not be adequately controlled despite intensive efforts to establish a tolerable, effective, and timely treatment[15].

The mothers and/or fathers or caregivers of the patients who received PS were contacted by telephone to invite them to participate voluntarily in the study; those who agreed to participate were given an informed consent form. Patients were excluded if informed consent could not be obtained, if their records were incomplete, or if they did not pass away during the study analysis period.

The variables recorded to characterize the patients were: biological sex (male/female), age at admission to PC (in months), and baseline oncologic diagnosis. The diagnoses were grouped into leukemias, solid tumors, and central nervous system (CNS) tumors. Regarding the use of PS, the following were recorded: the refractory symptom(s) that led to the indication, the presence of the indication in the medical record, and the agreement on this indication by the parents and/or the patient in the clinical record, the drugs used for PS, the time elapsed between the start of sedation and death (hours), and the place of death. The time elapsed between the start of PS and death was categorized as "less than 24 hours", "between 24 to 72 hours", and "more than 72 hours"[16,17].

Data were recorded anonymously in an MS Excel® spreadsheet and coded with numbers to facilitate data analysis and avoid possible typing errors. A descriptive analysis was performed using the mean and position measures for quantitative variables and absolute and relative frequencies for categorical variables, both for the total number of patients and separately according to oncologic diagnosis.

The study was approved by the Research Ethics Committee of the North Metropolitan Health Service. The parents/guardians of the patients included in this study agreed to participate after an informed consent process.

Results

Between 2003 and 2021, 204 patients were seen in the PC unit. Only 46 patients received PS (22.5%). Of this group, informed consent to participate was obtained for 36 patients. 7 patients were excluded since it was not possible to contact the primary caregiver and 3 patients because guardians/parents decided not to participate in the study (figure 1).

Table 1 shows the clinical and PS characteristics of the total number of patients and according to oncologic diagnosis. The mean age of the patients evaluated was 8 years 7 months, with a range between 9 months and 21 years 9 months. More than half of the patients were male (56%). Patients with solid tumors (hepatoblastoma, osteosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, rhabdomyosarcoma, lymphoma, germinal tumor, gastric tumor) required PS with the highest frequency (45%), followed by leukemias (36%) and CNS tumors (19%).

The refractory symptoms for the indication of PS were dyspnea, pain, anxiety, bleeding, vomiting, and seizure, with dyspnea being the most frequent symptom (50%) in the total group of patients. According to diagnosis, pain was the most frequent refractory symptom in the leukemia group (46%), and dyspnea was the most frequent in the solid tumor group (65%) and patients with CNS tumors (71%).

In 100% of cases, there was an indication for PS in the clinical record, associated with the record of verbal consent by the parents/caregivers of patients in PC.

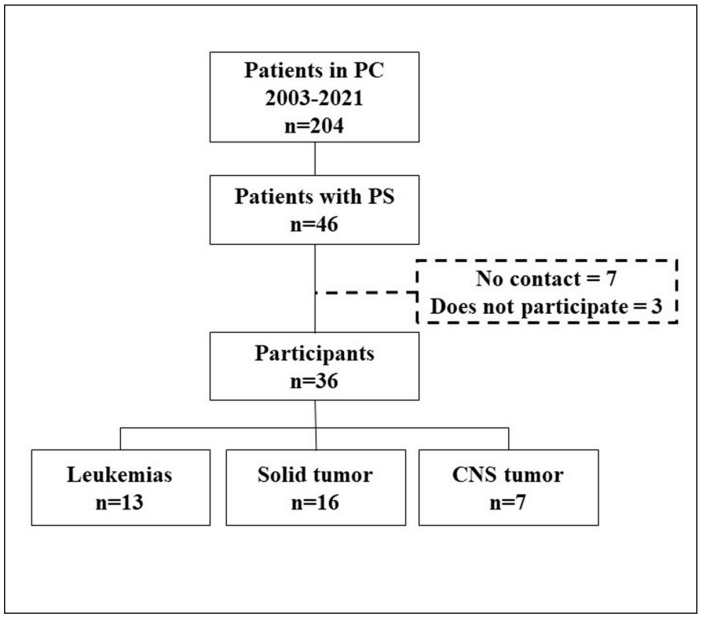

Figure 1. Participant flow chart. PC: Palliative Care. PS: Palliative Sedation. CNS: Central Nervous System.

Consent by the patients who received PS was recorded in 11% (4/36), with an age range between 14 and 21 years.

In 97% of the cases the drug used was intravenous midazolam in continuous infusion and in 22%, there was an association with the use of other drugs such as morphine and phenobarbital for the management of other symptoms. According to oncologic diagnosis, the concomitant use of other drugs was higher in children and adolescents with CNS tumors.

Regarding the time elapsed between the start of PS and death, most patients remained on PS for more than 72 hours (44%), with a mean of 70 hours, a minimum of 3 hours, and a maximum of 720 hours. According to oncologic diagnosis, most patients with leukemias and solid tumors remained on PS for more than 72 hours before death (38% and 50%, respectively), while most patients with CNS tumors died between 24 and 72 hours from the start of PS (57%) (table 1).

Regarding the place of death, 72% of the patients died in a hospital and the rest at home, with the support of the PC team (table 1). Most patients who died in the hospital died in the oncology center where the diagnosis of cancer was made (96%) and only one patient died in the hospital in the city of origin. It is noteworthy that no patient died in the Intensive Care Unit.

Discussion

Children and adolescents with oncological pathology at the end of life present multiple symptoms and in most cases, a significant associated suffering is described, both for the patient and her/his family, as well as for the treating team. It is at this stage of the disease that PC plays a fundamental role, providing a multidisciplinary perspective, covering not only the physical, but also the emotional, spiritual, and social dimensions in the management of these children. There is an increasing number of studies that show that early intervention by PC teams provides timely care to children and adolescents to favor the mourning process of parents and caregivers[4,12,18]. The current recommendation is to integrate these teams into Oncology Units, a model that has been implemented in our Unit since 2003.

In this context, PS is a tool in the management of refractory symptoms, and there are multiple publications in adults that have described its usefulness[6,19,20]. However, the literature on the pediatric population is scarce. In Latin America, we found 2 studies in relation to PS and pediatric PC, the one by González- Ronquillo[8] in Mexico (2013) and the one by Buitrago C. in Bogotá (2019)[9]. Both describe the importance of PS in the management of refractory symptoms but analyze

Table 1. Clinical characteristics and palliative sedation of the total number of participants and according to oncological diagnosis

	Oncological diagnosis			
	Leukemias n = 13 (36%)	Solid tumor n = 16 (45%)	CNS tumor n = 7 (19%)	Total n = 36
Age (months), average	119	100	88	104
Male sex, n (%)	7 (54)	9 (56)	4 (57)	20 (56)
Refractory symptoms associated with PS use, n (%)				
Pain	6 (46)	4 (24)	0	10 (28)
Anxiety	2 (15)	0	0	2 (5.5)
Dyspnea	2 (15)	11 (65)	5 (71)	18 (50)
Hemorrhage	2 (15)	0	0	2 (5.5)
Nausea/vomiting	1 (8)	2 (12)	0	3 (8)
Convulsions	0	0	2 (29)	2 (5.5)
Sedation time before death, n (%)				
< 24 hours	4 (31)	3 (19)	0	7 (20)
24 a 72 hours	4 (31)	5 (31)	4 (57)	13 (36)
> 72 hours	5 (38)	8 (50)	3 (43)	16 (44)
Place of death, n (%)				
Home	4 (31)	6 (38)	0	10 (28)
Oncology Hospital	9 (69)	10 (62)	7 (100)	26 (72)

PS: Palliative Sedation. CNS: Central Nervous System.

a few cases (2 and 17 patients, respectively). In Spain, the most recent study is from 2022[10], where 20 patients who received PS were evaluated. This publication describes that most pediatric health centers that received PS do so by extrapolating the experience of teams that care for the adult population.

In our study, 22.5% of the children and adolescents treated in PC received PS, which is similar to other publications that evaluate end-of-life oncology patients, such as the study by Maeda et al.[11], where 26% of PC patients required PS. In this same study, they describe that the most frequent oncologic diagnosis requiring PS was solid tumors, which coincides with our study.

A refractory symptom is considered one that cannot be adequately controlled despite aggressive efforts to identify a tolerable therapy[15,20], by an expert health care team, within a given period. It should be noted that all our patients were evaluated by a multidisciplinary team to determine that the symptom was refractory, using various therapeutic approaches, which are beyond the scope of this analysis.

In our study, pain and dyspnea were the most frequent refractory symptoms, as also described in the studies by Maeda[11] and Noriega[10], the latter with a more heterogeneous population than that described in ours. In addition, we observed a higher frequency of refractory dyspnea in children and adolescents with CNS tumors, while pain was more frequent in patients with leukemia and solid tumors. In the case of solid tumors, the presence of refractory symptoms related to tumor compression effect, such as nausea and vomiting, stands out, while in patients with leukemias and also in some cases of solid tumors, bleeding also appears as a refractory symptom which, despite not being a frequent symptom in all patients, should be considered when planning PC in these patients.

Different guidelines published in the adult population[6,11,21,22], describe that midazolam is one of the drugs of choice to sedate and control refractory symptoms, given its fast action and short half-life. This coincides with what was observed in this report, since it was the drug used in 97% of the cases, associating with phenobarbital only in those patients in whom the refractory symptom was seizures[20]. It is important to note that the patients were already receiving other drugs, mainly morphine, whose use was indicated for pain and dyspnea management, but not as a sedative. Almost all patients received PS through a central venous catheter, a device they used to receive chemotherapy in their ac-

tive treatment phase. However, it is important to point out that, in the absence of this route, the subcutaneous route can be used without complications and with good tolerance, which is considered the main route of drug administration in patients under PC[23].

Unlike what is observed in adults, agitation was not a frequently recorded refractory symptom in the pediatric population studied, being observed in only 2 patients (5.4%). The low frequency of this symptom in our study is similar to that described by de Noriega[10]. However, they emphasize that it was observed in concomitance with other symptoms, suggesting that the presence of agitation could be due to the interaction of the drugs used, rather than a primary refractory symptom in children with advanced cancer.

Although PS is a procedure indicated by the medical team, the recommendation is that it should always be agreed upon with the patient, if her/his condition allows it, and with the main caregivers since it implies disconnection and loss of interaction of the child with her/his affective environment[6]. A previous conversation was held with the families of all patients included in this study, with 100% documentation of the indication and assent for the procedure by children over 12 years of age. The decision to have an explicit document (PS informed consent) for this procedure is not a matter of consensus in the literature[7].

Before initiating PS, it has been suggested that the PC team evaluate with the patient and family the place where the PS will be administered, if required. In the review by Amrita[24], it is described that, in the adult oncology population, only 5-36% received PS at home. This is probably explained by the fact that hospitalized patients have a higher symptom burden than patients who remain at home while on PC. Korzeniewska-Eksterowicz[21] reported that, in the pediatric population, home PS was administered in only 20% of patients because, although home PS is safe, it requires constant communication and cooperation between the family and the PC team, which is not always achieved. In a review by Kiman[25], parents preferred the home as the place for their children to die, which implies a greater coordination effort to achieve this objective.

In our study, 72% of the patients who required PS died in the hospital due to the complexity of their symptoms, which entailed a great emotional burden for their caregivers, requiring hospitalization to address all the needs presented by the patients and their families. We believe that the development of PC units that can provide care 24 hours a day, 7 days a week, will have a positive impact on favoring the home death of these children.

Different studies show that the time elapsed between the start of PS and the patient's death varied in duration, from hours to days, and that even in studies in adults, it was observed that the average survival did not vary whether patients received PS or not[26,27]. However, the duration of survival should not be considered an indicator to evaluate PS, since the main objective of PS is to alleviate one or more refractory symptoms, regardless of the duration of sedation before death.

This study has certain limitations, such as the small number of patients included and the fact that retrospective records were used, so that there were variables that would have been interesting to analyze but could not be obtained. However, we believe that the main strength of this study is the period reviewed (18 years), which allows, despite the low frequency of the issue under study, to achieve a broad view of this clinical practice over time, considering, in addition, that it was the same team that was in charge of these patients and their families in the 18 years included in this review. In addition, the patients studied represent a homogeneous group, since they only corresponded to oncologic patients in PC, allowing us to obtain representative data of this reality. In addition, it should be noted that the PC Unit of our hospital was implemented in 2003 and has an interdisciplinary team, in constant training and education, and with vast experience in the management of cancer patients.

Conclusions

This study shows that PS in children and adolescents in PC for advanced cancer is a therapeutic tool that can be used in the pediatric population, which is indicated for refractory symptoms, allowing optimization of the management of patients at the end of life. The most frequent refractory symptom in this group was dyspnea, and the most frequently used drug was midazolam. In order to extrapolate this experience to children and adolescents who require PC for non-oncologic pathologies, it is necessary to carry out multicenter studies that include this patient population, which will allow us to identify different symptoms and clinical situations, and to reach a consensus on recommendations that guide the management of symptoms, the early recognition of refractory symptoms to be able to indicate PS at the appropriate time, generating technical bases for its use. We hope that the experience described can lay the foundation for building much-needed local evidence on this subject.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study

Financial Disclosure

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