PALLIATIVE SEDATION IN ADVANCED CANCER PATIENTS HOSPITALIZED IN A SPECIALIZED PALLIATIVE CARE UNIT

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ABSTRACT

Purpose: To describe the practice of palliative sedation (PS) in inpatients with advanced cancer in a specialized palliative care (PC) unit in Colombia.

Methods: Descriptive prospective study including all adults with cancer hospitalized under PS in a cancer institute between January and July 2015 in Colombia. Variables examined were: diagnosis; physical functioning; symptoms at the start of sedation; medications and dosages used; and type, level, and time of sedation. Descriptive and correlational statistics were obtained.

Results: Sixty-six patients were included, 70% of which were women. The patients had an average age of 61 years (range: 24-87), and 74% had a Karnofsky Index (KI) of 50% or less. The most frequent diagnosis was breast cancer (22%), and 82% had metastatic cancer. The prevalence of palliative sedation was 2% and the most common symptoms indicating it were dyspnea (59%), delirium (45%), and pain (32%). All patients received midazolam as a sedative. The average time between the interval start and culmination of sedation was 44 hours. There was a significant and inverse relationship between functionality and time under sedation.

Conclusions: Palliative sedation is a valid therapeutic option for refractory symptoms causing suffering. The results correspond to international reports and guidelines, which suggests that PS is tailored to the needs of the individual patient while maintaining a high scientific standard, even in a context where PC is under development. However, further development of strategies and clear indications toward the use of PS in Colombia are needed, given its still scarce use.

Keywords: palliative care, terminal care, deep sedation, evaluation of symptoms, neoplasia, cancer.

INTRODUCTION

Palliative care (PC) constitutes a multidisciplinary intervention based on a biopsychosocial and spiritual approach to improve the quality of life of patients with a terminal illness [1-3]. The objective of these measures is the prevention and relief of physical, social, and emotional suffering for both patients and their families [4]. Patients with cancer are often vulnerable because they have multiple symptoms of long evolution and variable origin that are not limited to those caused by the neoplasia [5-7]. Usually, a proper approach allows for controlling these symptoms. However, in some patients, these symptoms become uncontrollable [6]. As a last therapeutic resort, palliative sedation (PS) offers a management option for those patients in the terminal phase of the disease whose symptoms have become refractory to conventional management. Like any therapeutic tool, there are clear indications for use, which are framed in the context of intractable symptoms that cause suffering [6].

In 2010, the European Association of Palliative Care defined PS as "the monitored use of medications intended to induce a state of decreased or absent awareness (unconsciousness) in order to relieve the burden of otherwise intractable suffering, in a manner that is ethically acceptable to the patient, family and health care providers" [7-15]. The prevalence of PS varies considerably in the studies reported, especially in terms of initiation and the definition and methodology used. Most studies have been conducted in hospices where the prevalence varies between 3.1% [16] and 51% [17]. In hospitalized patients, Stone et al. [18] reported a prevalence of 26%, whereas Menten et al. [16] reported a prevalence of 1.33%. In the Latin American context, only a study conducted in Uruguay reported a prevalence of 23,5% [19] indicating that, in most countries of the region (including Colombia), studies to determine the use of PS are scarce.

Within the intractable symptoms that indicate the use of PS, studies have identified delirium, dyspnea, and pain as some of the main symptoms [10,19-23]. Current evidence shows that PS does not accelerate or interfere with the timing and process of dying. In fact, a small number of patients under sedation have a small increase in survival, even though this result is not the intention or goal [6,25-27]. Given these findings, one of the major differences between PS and euthanasia can be inferred: in the latter, the goal is death of the patient, whereas in PS, the goal is control of symptoms under a decreased state of awareness [25, 28-30].

Current clinical evidence on PS as a therapeutic option for the situations described above supports its use both ethically and medically. However, most of this information is derived from developed countries with

many decades of experience in specialized and well-organized PC. While Colombia is a pioneer in PC in Latin America its development and access is still limited, and misconceptions related to its practice persist [32]. Yet, the country´s human and pharmacological resources for the management of patients with advanced diseases is growing. Unfortunately, to date no study has been conducted to determine the prevalence and clinical characteristics of PS. Furthermore, it is unknown whether the application of PS, which is extrapolated from international guides, conforms to Colombia's population and local needs. Therefore, the aim of this study was to describe the sociodemographic and clinical characteristics of a group of cancer patients as well as prevalence, indications, time, and medications used for PS at a specialized PC unit at a cancer institution in Medellin, Colombia.

METHODOLOGY

Design

A descriptive prospective study was designed for patients over 18 years of age who were hospitalized with the diagnosis of cancer and started PS between January and July of 2015 at the Instituto de Cancerología, Clínica Las Américas, a referral center for oncology patients in the upper west region of Colombia. The study was previously approved by two independent review boards (the university ethical committee and the institutional ethical committee).

Data collection instrument

A data collection instrument was designed that included demographic data and clinical information such as baseline diagnostics; Karnofsky index (KI) and symptoms for which medical care was requested; information on the implementation of PS, such as the PS indication, drugs used prior to PS, drugs and dosages used in PS at the beginning and end of the treatment, sedation level according to the Ramsay scale [33], type of PS (intermittent or continuous), and start and end times of sedation. Clinical history was used exclusively as a secondary source of information; patients and their families were not approached nor was verbal information provided by health personnel. The study was approved by the institutional Ethics Committee.

Procedure

The healthcare team considered the use of PS when patients experienced one or more refractory symptoms (physical, psychosocial or spiritual symptoms that did not respond to optimal treatment by the multidisciplinary team), and when it caused significant suffering, as expressed by them or as detected by

the family and/or the healthcare team members. Then, the specialist would put under consideration the option and type of sedation and discuss it with the patient and/or the family. Sometimes this option was previously discussed in the course of the treatment. Once the patient (when possible) or family gave consent for the initiation of PS, the specialist defined the start of PS. The identification number and clinical history of the patient were reported to the research group and one of the researchers immediately began monitoring the treatment and recording the data.

Data Analysis

The collected data were stored in an Excel database and analyzed with the Statistical Package for Social Sciences SPSS 20.0. Descriptive statistics and nonparametric-type statistics were obtained given the non-normal distribution of the samples between the following variables: age, KI, time under sedation, principal drug doses for the PS at the beginning and end of treatment, and initial and end scores of the Ramsay scale.

RESULTS

Sixty-six patients requiring PS were included. Forty-six patients (70%) were women; the average age was 61 years (SD: 14.2; range: 24-87), and 52 patients (74%) had a KI of 50% or less. The most frequent diagnosis was breast cancer (22%), and 51 of the patients (81.8%) had metastatic cancer (Table 1).

During the study period, a total of 2890 patients were attended by the PC team but only 66 required PS, resulting in a prevalence of 2.2%.

*Include Table 1 here

At the emergency room intake, 33 patients (50%) cited pain as the reason for consultation. The main refractory symptom that indicated PS initiation was dyspnea (59.1%), followed by delirium (45.5%) and pain (31.8%). More than half of the patients had more than one refractory symptom (60.1%).

Nine patients (13.6%) presented with existential suffering, but of these, only one referred to it as the only symptom; the rest of the patients had other symptoms such as pain, delirium, or dyspnea, which ultimately indicated PS (Table 2).

*Include Table 2 here

The drug used for PS in all cases was midazolam with a mean initial dose of 48.4 mg/day (SD: 54.8 mg/day; range: 8-384 mg/day) and a final average dose of 100.4 mg/day (SD: 97.42 mg/day; range: 0-480 mg/day).

Ninety-one percent of the patients required adjuvant drugs with morphine as the most commonly used drug (75.8% patients) at a dose of 64 mg/day average (12-240 mg/day) at the start of PS and 113 mg/day (20-480 mg/day) at the end of PS; the second opioid used was hydromorphone with a frequency of 7.6% (5 patients). No other opioids were used (Table 3).

*Include Table 3 here

Two types of sedation were used according to the severity of the illness, the medical indication, or the preference of the family: intermittent (using scheduled midazolam at a 4 to 8-hour interval) and continuous (use of midazolam in continuous infusion). Intermittent sedation was initially chosen when refractory symptoms where not continually present and/or when the patient or the family expressed their preference towards this kind of sedation. Continuous sedation was initiated when refractory symptoms were very frequent causing significant suffering or when the patient or the family preferred this type of sedation. Both types of sedation were titrated until symptom control was achieved. Of the total patients who required intermittent sedation at the beginning (n=39), only 48% continued with it; the remaining patients required an escalation to continuous sedation (Figure 1).

*Include Figure 1 here

Causes that led to complete PS were death in 64 patients (97%) and the control of symptoms in two patients (3%): one patient experienced dyspnea and the other experienced delirium. The average survival time after the start of PS was 44.9 hours (SD: 41.1; range: 1.3-215).

The relationships between age, KI, time under sedation, doses of midazolam at the beginning and end of treatment, and initial and end score of the Ramsay scale were examined using the statistical Spearman's Rho (see Table 4). An inverse and significant relationship (although of low to moderate force) between the KI and the total hours under PS ($p < 0.01$) was found. Given the particularity of the finding, an ANOVA was conducted to examine whether there were differences according to the level of KI reported,

finding that the differences were statistically significant ($F=5, 327$; $p<0.01$, excluding an extreme case; see Figure 2).

A significant and inverse relationship was found between the initial dose of midazolam and total hours of PS ($p<0.05$) and between the Ramsay score at the beginning and final doses of midazolam ($p<0.01$). A positive and significant correlation (of moderate force) was found between the initial and final doses of midazolam ($p<0.01$) and between the final Ramsay score and final dose of midazolam ($p<0.05$; see Table 4). Despite the statistical significance of these relationships, it should be noted that they were not of high intensity.

*Include Table 4 here

*Include Figure 2 here

DISCUSSION

When analyzing the practice of PS in a group of patients treated at a national referral cancer institution in Medellin, Colombia, it can be deducted that the characteristics of the population, such as indications, form of use, and expected results of this treatment, are consistent with the results from other populations. However, its prevalence is low in comparison to other reports [16-19] probably due to adequate symptom control in the unit (because of early referral practices in the institution, a healthcare multidisciplinary team trained at a specialist level in PC, and an individualized treatment based on clinical guidelines). Other reasons might include the moderate development of PC in our country and in Latin America in general, as well as misconceptions regarding PS; however, given the data available in this study and the scarcity of other studies about PS in these contexts, it is not possible to extract conclusions of this type. Further studies on the prevalence of PS and aspects related to its practice in Latin America and other developing regions would be needed.

Regarding the demographic characteristics of the population studied, two-thirds of the population were female and 20% of the patients had breast cancer, possibly because breast cancer remains one of the main causes of morbidity in Colombian women, as reported by the National Cancer Institute [34].

Of the patients requiring PS, 81.8% had cancer with advanced stages of metastatic compromise, indicating that PS was used as a resource in patients with advanced disease in the terminal phase. In more

than 60% of the patients, a KI lower than 50% was found, which denotes great functional compromise at the start time of the PS treatment; this result coincides with that of Mercadante et al., whose home PS study reported a KI of 57.5 ± 18.7 [14].

Of our population, 5% had a KI above 60%; however, the severity of symptoms and their refractory nature required PS as a last therapeutic resort. From this result, it can be inferred that the index of functionality is not directly related to the need for PS, which is why it is not part of the criteria for defining initiation of PS, even though it is an important prognostic factor [14,37-38].

The main symptoms indicating PS were dyspnea, delirium, and pain. These results are consistent with those found in the review of Maltoni et al. [20], where the most common symptoms were delirium (30%), psychological stress (19%), dyspnea (14%), and pain (7%). It should be noted that when psychological stress is mentioned, its prevalence varies significantly in different studies, from 0 to 40%, possibly due to its unclear definition and the difficulty in identifying when to consider it refractory [10,19,20]. It is salient that pain was the leading cause of admission to the hospital but was the third cause for the indication of sedation, which suggests that the current broad analgesic therapeutic repertoire allows for better control of this symptom.

All the patients were sedated with midazolam, a result comparable to that found in the literature where it is reported as the most commonly used drug [9,10,20,24]. Midazolam is the drug of election for PS in most guidelines [40] and in the institution were the study was conducted. Arguments in favor are its high potential for sedation, a low risk of respiratory depression at sedative doses, a wide safety margin, its short half-life, its more immediate titration responsiveness, it also can be administered both subcutaneously and intravenously, and finally, there is considerable experience of its use in PS [7,8].

The average daily dose of midazolam at the beginning and end of the PS was moderately higher than the average reported in other studies, but the range of the daily dose is within the recommended doses; for example, Claessens et al. [6] determined a range between 1 and 450 mg/day, values correspond to those suggested in the PS guide of the European Society for Medical Oncology where the maintenance dose ranges from 24 to 480 mg/day [6-8,40].

More than half of the patients began with intermittent PS, but as they began to require a gradation of their doses, the interval began to shorten until the symptom was controlled; by the end of the sedation, more than half of the patients ended up receiving continuous PS. Also, when presented with the two options

(intermittent vs. continuous sedation) and their rationale, some patients expressed their preference for either one. However, almost half of patients who initiated with intermittent sedation had to be scaled to continuous sedation because symptom control was not achieved, and significant suffering was detected; in these cases, the patient or the family gave their consent. Schildmann et al. [40], in a systematic review published in 2015, found that the vast majority of articles recommended starting with an initial loading dose and, according to the response, leaving a maintenance dose through infusion to achieve better control, according to individual requirements.

Almost all the patients ended PS due to death during the treatment, but the PS treatment was withdrawn from one patient with dyspnea and other patient with delirium because symptom control was achieved, reflecting that the intention of PS was symptom control. However, it is expected that patients in the terminal phase of disease and with refractory symptoms will have short survival times, as these factors contribute to bad prognosis, as demonstrated in other studies [38,41]. Survival time after the start of PS was an average of 2 days with a minimum of 1 and a maximum of 9; these times are consistent with the times described in most studies [10,20], except in the study reported by Morita et al. [34], which indicates survival of up to 3 weeks.

When examining the correlation between the variables KI and sedation time, it was found that to lower functional levels more time was spent under sedation, although it would be expected that those patients with greater functional alteration would have a shorter life expectancy during the sedation [38,41]. This finding is important because it confirms the aforementioned notion concerning the intent of PS, where the main goal is to control symptoms and not to accelerate the process of death. Indeed, Maltoni et al. [42] have reported that there is no significant difference in the survival of those patients under PS compared with those who are not sedated and even found a trend toward an increase in survival in patients under PS [20].

A significant and inverse relationship between the dose of midazolam and sedation time was found. It is possible that, when dealing with symptoms that are difficult to manage and of greater severity, a more intensive treatment is required, which in turn is related to increased mortality [38,41,43]. Similarly, a direct relationship between the doses of midazolam and the Ramsay score and between the initial and end doses of midazolam were found, which was to be expected, as the goal is to achieve an appropriate level of sedation to control refractory symptoms. In this regard, patients who require greater initial doses will

usually require more doses at the end of the sedation. It should be noted that there is no clear consensus on the ideal dose for sedation, possibly due to the absence of high quality studies [40].

The main limitation of this study is that the characterization of the practice of PS was conducted in a single PC center in a single city in Colombia. Also, the cross-sectional nature of the study does not allow understanding the relationship between symptoms at hospital admission and symptoms indicative of PS, or to determine factors that contribute to symptoms becoming refractory thus indicating the use of PS. Future research should generate national multi-center studies to achieve a complete characterization of this practice in the Colombian population and to determine which patients would beneficiate more from this therapeutic option.

To our knowledge, this is the first study in Colombia and one of the few in Latin America that specifically characterized the use of PS in a hospitalized oncological population of advanced age. The results match those reported in other populations worldwide, which suggests that PS is a practice focused on the needs of the human being rather than the scientific technology available and that it is possible to aid in the process of a peaceful death. These results encourage further development of strategies and clear indications toward the use of PS in developing contexts, given its still scarce use.

Finally, within the use of PC and under the ethical precepts that govern it, PS is a valid therapeutic option against refractory symptoms that cause suffering in patients with chronic terminal cancer or other terminal diseases also in developing countries such as Colombia.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ETHICAL APPROVAL

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Formal consent was not required.

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