








Assessment of pain control in advanced cancer patients admitted to a palliative care unit

Avaliação do controle da dor em pacientes com câncer avançado internados em uma unidade de cuidados paliativos

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ABSTRACT

Introduction: Pain in people with cancer is prevalent and should have an individualized therapeutic plan.

Objectives: To evaluate pain control in advanced cancer patients in a hospital palliative care unit.

Methods: This is a cohort study, with prospective design, and quantitative approach, including advanced cancer patients admitted to a palliative care unit between June 2021 and February 2022 reporting pain. Data was collected from medical records and the Brief Pain Inventory (BPI) was used to assess pain on the first (D1), third (D3) and seventh (D7) day of hospitalization.

Results: One hundred and four patients participated in the study. The most prevalent tumors were of the gastrointestinal tract (n=23; 22%), cervix (n=21; 20%) and breast (n=17; 16%). Abdomen was the most reported site of pain (n=34; 33%), with 50% classified as nociceptive pain, 39% neuropathic pain, and 11% mixed. On D1, 43% reported severe pain, 31% moderate, and 12% mild pain. There was an evolutionary drop in the percentage of severe pain (BPI3 70% to 37.1%; BPI4 12.6% to 5.4%; BPI5 42.5% to 13.5%; and BPI9 67.8% to 21.6%) according to the answers to all BPI questions during the period. On D1, D3 and D7, the average equipotent doses of oral morphine were 116 mg, 133 mg and 154 mg and the frequency of use of adjuvant use was 60%, 75%, and 69%, respectively.

Conclusions: Pain was properly controlled and was related to the increased use of adjuvants, both for general and neuropathic pain. It was possible to observe that the use of adjuvants was related to better pain control.

Keywords: Palliative Care; Pain; Inpatient Care Units; Neoplasms.

RESUMO

Introdução: Dor na pessoa com câncer é prevalente e deve ter um plano terapêutico individualizado.

Objetivos: Avaliar o controle de dor em pacientes com câncer avançado em uma unidade hospitalar de cuidados paliativos.

Métodos: Trata-se de estudo do tipo coorte, delineamento prospectivo e abordagem quantitativa, incluindo pacientes com câncer avançado internados em uma unidade de cuidados paliativos entre junho de 2021 e fevereiro de 2022 com presença de dor. Foram coletados dados de prontuário e aplicado *Brief Pain Inventory* (BPI) para avaliar a dor no primeiro (D1), terceiro (D3) e sétimo dias de internação (D7).

Resultados: Participaram do estudo 104 pacientes. Os tumores mais prevalentes foram do trato gastrointestinal (n=23; 22%), colo de útero (n=21; 20%) e mama (n=17; 16%). Abdome foi o local mais relatado de dor (n=34; 33%), sendo 50% classificada como dor nociceptiva, 39% neuropática e 11% mista. No D1, 43% relataram dor intensa, 31% moderada e 12% leve. Observou-se evolutivamente queda no percentual de dor intensa (BPI3 70% a 37,1%; BPI4 12,6% a 5,4%; BPI5 42,5% a 13,5%; BPI9 67,8% a 21,6%) conforme respostas às perguntas do BPI no período. No D1, D3 e D7, as doses médias equipotente de morfina oral foram, 116mg, 133mg e 154mg e a frequência de uso de adjuvantes 60%, 75% e 69%, respectivamente.

Conclusão: A dor obteve controle adequado e apresentou relação com o aumento do uso de adjuvantes, tanto para dor geral, quanto neuropática. Foi possível observar que o uso de adjuvantes esteve relacionado ao melhor controle algico.

Palavras-chave: Cuidados Paliativos; Dor; Unidades de Internação; Neoplasias.

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INTRODUCTION

Pain in people with cancer is present in 59% of patients undergoing treatment and 64% in those with advanced disease, when specific cancer treatment is no longer indicated¹. It is one of the most disabling and dreaded symptoms of cancer and is often inadequately treated, causing great damage to quality of life². In general, cancer-related pain is multidimensional, including physical, psychosocial, and spiritual aspects. For this reason, treatment should include an individualized therapeutic plan, with multi-professional participation².

In 1986, based on evidence of poor management of cancer pain, due to the reluctance of health professionals, institutions, and governments to use opioids for fear of addiction, tolerance and illegal abuse, the World Health Organization (WHO) published a set of guidelines for the treatment of this symptom based on the three-step analgesic ladder. The main aim of this publication was to legitimize the prescription of strong opioids. Today, the correct use of the WHO method continues to be of great importance and should be encouraged, as it can lead to adequate long-term pain control in the majority of advanced cancer patients³.

The treatment of cancer-related pain should provide symptom relief with tolerable side effects. These treatments can be classified into pharmacological, non-pharmacological and interventional therapies. In this context, adjuvant drugs are medications that are not primarily indicated for pain control but can have an effective analgesic effect in various pain syndromes, especially in cases of neuropathic pain.¹ Interventional therapies are available to treat pain in cases refractory to systemic analgesics and cases where side effects are intolerable, limiting the use of medication².

According to the International Agency for Research on Cancer (IARC), the incidence of the disease is expected to increase by around 75% over the next two decades. This increase will have repercussions on the demand not only for clinical experience in treating cancer itself, but also for knowledge about managing the symptoms caused by the disease, especially pain. It is not possible to offer adequate treatment to patients without mastering the therapeutic approach to pain⁴.

Pain is an important cause of hospitalization in advanced cancer patients and its presence and management delay may be associated with longer hospital stays⁵. Thus, considering the need to better elucidate the issues involved in pain treatment of advanced cancer patients in palliative care, in order to document and evaluate the current clinical practice applied, the aim of this study was to evaluate pain

control in advanced cancer patients in a hospital palliative care unit.

METHODS

This is a prospective cohort study with a quantitative approach, which included all patients presenting pain admitted to the exclusive palliative care unit of the Brazil's National Cancer Institute (INCA) between June 2021 and February 2022. The protocol for this study (Figure 1) was approved by INCA's Research Ethics Committee, under decision number 4,729,007 of 24 May 2021.

The inclusion criteria were being 18 years old or older, being admitted to the unit, having the symptom pain associated or not with cancer, being lucid, agreeing to take part in the research and signing the Informed Consent Form (ICF). Participants who had difficulty communicating, disorientation or lack of reason, symptoms that were decompenated enough to interfere with their answers, as well as those who refused to take part in the study were excluded from the research.

Data collection

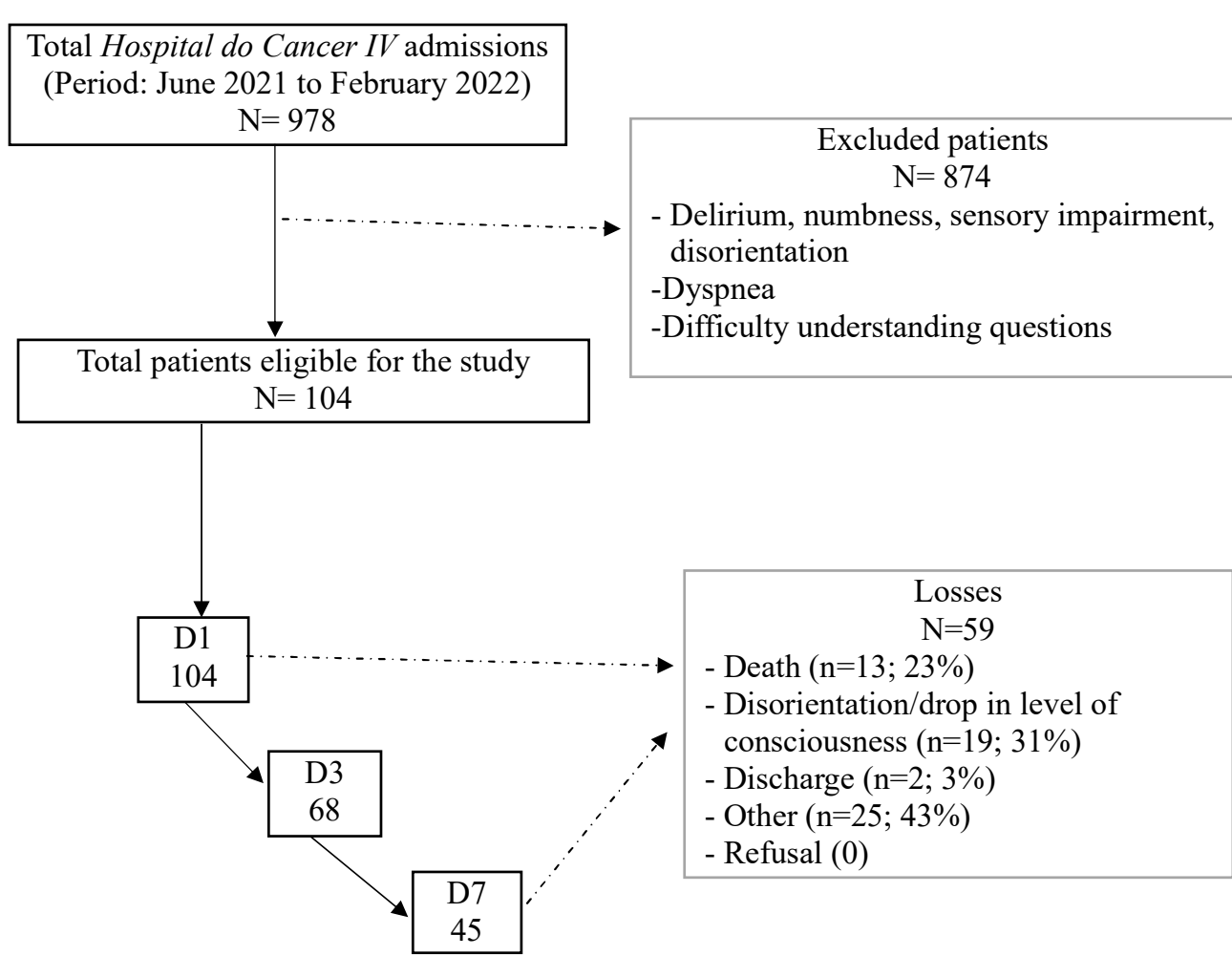
Data was collected through face-to-face interviews with the patient and by consulting their physical and electronic medical records by trained researchers on the first (D1), third (D3) and seventh (D7) days of hospitalization.

The socioeconomic and demographic variables taken into account were those relating to D1, i.e. the baseline of the study: age, gender, skin color, marital status, and level of education.

Clinical data was collected on the first assessment (D1) by consulting the physical and electronic medical records, taking into account: primary tumor location, presence of local and distant metastasis, type of previous cancer treatment, including surgery, chemotherapy, radiotherapy and hormone therapy, presence of comorbidities [systemic arterial hypertension (SAH) and diabetes mellitus (DM)] and the Karnofsky Performance Status (KPS).

The qualitative assessment of pain was carried out in a direct interview with the patient by an examiner trained and technically qualified for this assessment, and classified as neuropathic, somatic nociceptive, visceral nociceptive or mixed⁶. Additional characteristics were questioned and included association with movement, location, duration, and the presence of a possible second site of pain. Such pain characterization was only carried out on D1.

The Brief Pain Inventory (BPI)^{7,8}, an instrument translated and validated for Brazil, was used to quantitatively assess pain on D1, D3, and D7. To analyze the data, we chose four questions addressed in the BPI: strongest pain in the last



Note: N = number of observations.

Figure 1. Study patient selection flowchart.

24 h (BPI 3), weakest pain in the last 24 h (BPI 4), a number that, on average, best represents pain in the last 24 h (BPI 5) and divided the eleven BPI response options into four groups according to the degree of pain (zero – no pain; one to three – mild pain; four to six - moderate pain; and seven to ten – severe pain).

Medicines with analgesic effect were obtained by consulting the prescriptions in D1, D3 and D7, including common analgesics (dipyrone, paracetamol), non-hormonal anti-inflammatories (diclofenac, tenoxan), weak opioids according to the WHO Analgesic Scale (codeine, tramadol), strong opioids according to the WHO Analgesic Scale (morphine, transdermal fentanyl, methadone, oxycodone), and adjuvants (gabapentin, pregabalin, amitriptyline, venlafaxine, sertraline, citalopran and baclofen), as well as intravenous lidocaine and ketamine. Haloperidol and dexamethasone were not considered in this study as adjuvant drugs because they have different indications for advanced cancer patients and it could, thus, introduce bias to the analysis. It should be noted

that the limitation to these drugs is due to standardization in the unit where the study was carried out. Opioid doses were converted into an equipotent dose of oral morphine¹.

Sampling

Sampling was by convenience, i.e., based on the number of patients being followed up during the study period. However, to check our sampling power, we used a post hoc test from <https://clincalc.com/Stats/Power.aspx>, considering that the prevalence of pain was around 64%. Therefore, based on dichotomous results for two independent groups, with an alpha error of 0.05, a sample power of 98.9% was calculated for this study.

Data analysis

The data was analyzed using STATA software version 15.0. The Kolmogorov-Smirnov test was used to assess the data distribution of the variables. Parametric numerical variables were described as mean and standard deviation and non-parametric variables as median and interquartile range

(25th–75th percentiles). Categorical variables were described as absolute frequency and relative frequency as percentages. We used the chi-square test for proportions and to compare the frequency of pain, according to intensity, throughout the study and Spearman's correlation to assess the correlation between BPI and morphine dose.

RESULTS

A total of 104 patients took part in the study (Figure 1), the majority of whom were <60 years old (63.46%), female (65.38%) and white (44.27%). The most frequent primary tumor sites were gastrointestinal tract (22.11%), cervix (20.19%) and breast (16.35%). The majority had distant metastases (77.88%) and had received previous treatment (84.61%) (Table 1).

As shown in Table 2, the most frequent location of pain was the abdomen (32.69%), followed by the lower limbs (14.42%) and the chest (11.54%). The most common pain characteristics were spontaneous pain (67.31%) and localized pain (65.66%). Regarding the type of pain, 50.00% of the patients had nociceptive pain (including somatic and visceral types) and 39.42% had neuropathic pain. Only 10.58% had mixed pain.

Table 3 shows the intensity of pain reported by patients from D1 to D7 according to the BPI. The strongest pain in the last 24 h (BPI 3) was moderate or severe in 85.58% of patients. When asked which number on average best represents their pain in the last 24 h (BPI 5), 11.54% of patients reported mild pain, 30.77% moderate, and 43.27% severe pain. There was a statistically significant difference of pain intensity over the course of the study, with an increase in the percentage of absent pain and a reduction in severe pain (p -value < 0.050).

Figure 2 shows the variation in pain (all types) intensity according to questions three, four, five, and nine of the BPI over the seven days of the survey. In general, there was a significant drop in the percentage of severe pain and an increase in the percentage of absent pain according to the answers to all the BPI questions evaluated during the period (BPI3 70.0% to 37.1%; BPI4 12.6% to 5.4%; BPI5 42.5% to 13.5%; and BPI9 67.8% to 21.6%).

Of the 104 patients who started the study on D1, 68 continued on D3 and 45 on D7. Most of the losses were due to death or clinical worsening or changes in the level of consciousness (52.78%), as described in Figure 1.

According to Table 4, considering all types of pain, the average daily dose of opioid converted into oral morphine following analgesic equipotency was 115.64 mg on the first day, 132.50 mg on the third day, and 153.50 mg on the seventh day. The use of adjuvant medication was observed in 80.49% of those surveyed on D1, 85.18% on D3, and 87.50%

Table 1. Sociodemographic and clinical characteristics of advanced cancer patients with pain symptoms at the beginning of their hospitalization in a palliative care unit (N= 104).

Variables	Total N (%)
Age (years old)	53.6 (±14.1) [mean and standard deviation]
<60	66 (63.46%)
>60	38 (36.54%)
Gender	
Male	36 (34.62%)
Female	68 (65.38%)
Skin color	
White	45 (43.27%)
Black	17 (16.35%)
Brown	42 (40.38%)
Marital status	
Married/Stable union	49 (47.12%)
Other ^a	55 (52.88%)
Education ^b	
Illiterate	6 (5.77%)
Primary/Primary I	39 (37.50%)
Primary/Elementary II	25 (24.04%)
High school	34 (32.69%)
Primary tumor site	
Gastrointestinal tract	23 (22.11%)
Cervix	21 (20.19%)
Breast	17 (16.35%)
Head and neck	6 (5.77%)
Connective bone tissue	6 (5.77%)
Lung	5 (4.81%)
Non-melanoma skin	4 (3.85%)
Thyroid	1 (0.96%)
Prostate	1 (0.96%)
Other	20 (19.23%)
Distant metastasis	
No	23 (22.12%)
Yes	81 (77.88%)
Previous treatment	
No (virgin)	16 (15.38%)
Yes, palliative	60 (57.69%)
Yes, curative	11 (10.58%)
Yes, both	17 (16.35%)
Comorbidities	
Hypertension (Yes) ^b	23 (22.12%)
Diabetes mellitus (Yes) ^b	11 (10.58%)
KPS (%) [median and interquartile range]	30 (30-40)

Note: N = number of observations; % = Karnofsky Performance Status. ^adivorced/widowed/single; ^bvariable with missing data.

Table 2. Pain assessment of advanced cancer patients with pain symptoms on the first day of hospitalization in a palliative care unit (N= 104).

Variables	Total N (%)
Duration (days)	52.3 (±6.2) [mean and standard deviation]
Site of pain	
Abdomen	34 (32.69%)
Lower limbs	15 (14.42%)
Thorax	12 (11.54%)
Lumbar spine	11 (10.58%)
Pelvis	7 (6.73%)
Thoracic spine	4 (3.85%)
Other	21 (20.19%)
Features	
When moving	23 (22.12%)
Spontaneous	70 (67.31%)
At the end of the dose	11 (10.58%)
B Features	
Localized	65 (65.66%)
Irradiated	34 (34.34%)
Type	
Somatic nociceptive	26 (25.00%)
Visceral nociceptive	26 (25.00%)
Neuropathic	41 (39.42%)
Mixed	11 (10.58%)
Pain in another location	
No	59 (58.42%)
Yes	42 (41.58%)
Duration of the second pain (days)	34.0 (±3.6) [mean and standard deviation]

on D7. When excluding Haloperidol and Dexamethasone, these drugs were used by 59.61% of those surveyed on D1, 75.00% on D3, and 68.89% on D7. Considering only patients with neuropathic pain, the average dose of opioid converted to oral morphine was 115.20 mg on the first day, 139.25 mg on the third day, and 153.10 mg on the seventh day.

Among the patients included in the study, none received intravenous lidocaine, ketamine, or underwent an invasive procedure or radiotherapy for pain control.

During the data analysis, it was possible to demonstrate an inversely proportional relationship between the increased mean equipotent dose of oral morphine over the days of the study and reduced pain intensity (using response five of the BPI), with correlation coefficients of less than one, both in the analysis of general pain and neuropathic pain. Moreover, there was also an inversely proportional relationship between increased frequency of adjuvant use and reduced pain in-

Table 3. Percentage of patients according to pain intensity throughout the study according to BPI (N = 104).

Variables	D1	D3	D7	p-value
	%	%	%	
Strongest pain in the last 24 h (BPI 3)				
Absent (0)	5.8	28.5	28.0	0.010
Mild (1-3)	8.6	10.0	13.0	
Moderate (4-6)	17.3	24.0	22.3	
Intense (7-10)	68.3	43.2	37.1	
Weakest pain in the last 24 h (BPI 4)				
Absent (0)	44.0	55.0	62.0	0.005
Mild (1-3)	25.3	25.0	24.3	
Moderate (4-6)	18.4	16.7	8.1	
Intense (7-10)	12.6	3.3	5.4	
Average pain in the last 24 h (BPI 5)				
Absent (0)	16.0	35.0	37.8	0.012
Mild (1-3)	12.6	16.7	13.5	
Moderate (4-6)	28.7	31.7	37.8	
Intense (7-10)	42.5	16.7	13.5	

Note: N = number of observations; % = frequency; BPI = Brief Pain Inventory; D1 = first day of hospitalization; D3 = third day of hospitalization; D7 = seventh day of hospitalization.

tensity, with correlation coefficients of less than one, both in the analysis of general pain and neuropathic pain (Table 5).

DISCUSSION

This study sought to assess pain control achieved during the first week of hospitalization of advanced cancer patients in a specialized palliative care unit, evaluating the response according to the type of pain and drug class used. There was efficient pain control over time in the population studied and the increased use of adjuvants seems to be temporally related to better pain control, appearing to be an effective drug class for early pain control in advanced cancer patients.

The study's strengths include its prospective nature, the use of a validated and standardized scale directly for patients, the classification of pain by qualified and trained professionals to standardize data collection, and the fact that it was carried out in a large center where prescribers seem to have expertise in the pharmacological management of pain (which favors the use of various drugs in addition to opioids and common analgesics).

The data found is similar in many ways to a study carried out in the same hospital in 2016 (at that time, with data collected from medical records and focusing on pain management), namely: population profile, equipotent dose

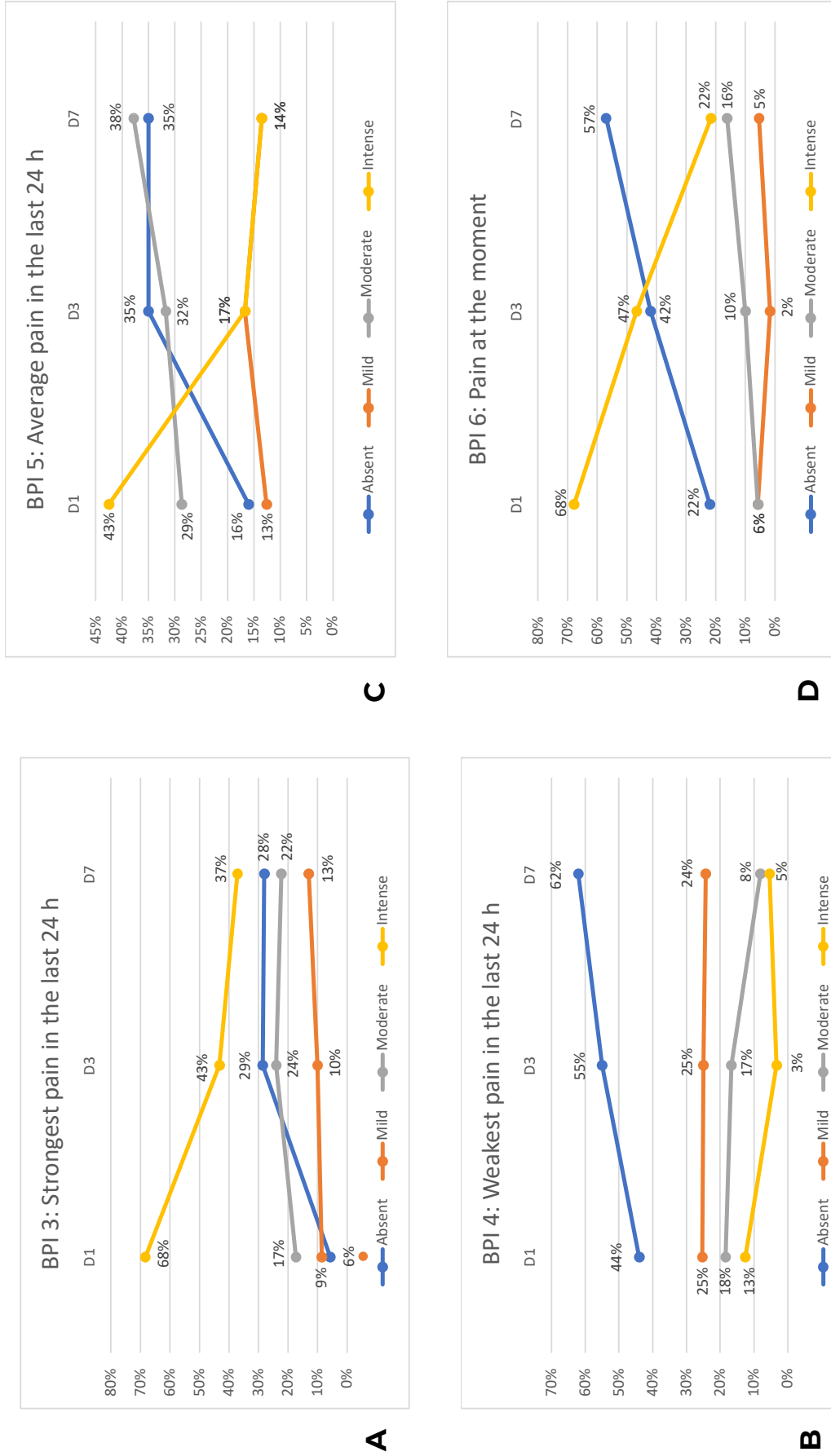


Figure 2. Variation of pain intensity (all types) according to questions A) three - strongest pain in the last 24 h, B) four - weakest pain in the last 24 h, C) five - average pain in the last 24 h, and D) six - pain at the moment, of the BPI over the seven research days in advanced cancer patients.

Table 4. Frequency of common analgesics and adjuvants use and average daily equipotent dose of morphine used by advanced cancer patients included in the study.

Use of drugs with analgesic effect	Patients with any type of pain			Patients with neuropathic pain		
	D1 (N = 104)	D3 (N = 68)	D7 (N = 45)	D1 (N = 41)	D3 (N = 27)	D7 (N = 16)
Common analgesic	92 (88.46%)	65 (95.59%)	39 (86.67%)	38 (92.68%)	25 (92.59%)	16 (100%)
Adjuvants*	62 (59.61%)	51 (75.00%)	31 (68.89%)	33 (80.49%)	23 (85.18%)	14 (87.50%)
Oral morphine equipotent daily dose (mg) (mean/median)	115.64 / 74.00	132.30 / 83.50	153.50 / 83.50	115.20 / 72.00	139.25 / 80.50	153.10 / 80.50

Note: N = number of observations; % = frequency; D = day.

*The following drugs were considered adjuvants: gabapentin, pregabalin, amitriptyline, sertraline, citalopran, venlafaxine, and baclofen.

Table 5. Correlation between the average dose of morphine and pain intensity and between the use of adjuvants and pain intensity in advanced cancer patients included in the study.

Day	Patients with any type of pain			Patients with neuropathic pain				
	BPI 5 correlation coefficient and morphine use	p-value	BPI 5 correlation coefficient and adjuvant use	p-value	BPI 5 correlation coefficient and morphine use	p-value	BPI 5 correlation coefficient and adjuvant use	p-value
D1	0.49	0.077	0.37	0.091	0.25	0.074	0.26	0.067
D3	0.25	0.042	0.33	0.032	0.37	0.016	0.35	0.021
D7	0.41	0.005	0.36	0.011	0.31	0.010	0.34	0.011

Note: D = day; BPI = Brief Pain Inventory.

of oral morphine (117 mg/d in 2016 and 115 mg/d on D1), common analgesic use (85.30% in 2016), frequency of adjuvant use above that described in other studies (37.6% in 2016, excluding neuroleptics and corticosteroids)⁹. These findings may suggest a high degree of stability in the profile of patients admitted to the unit and training for prescribing professionals.

The population of this study is similar to that studied in an oncology ward of a university hospital in the Northeast of Brazil, with a predominance of women (65.3%) in its majority aged under 60 years old (58%)¹⁰. This study found 66.67% of women and 64.37% of people under the age of 60.

In a four-year cohort study carried out in Australia, of the 1,800 patients assisted in palliative care services, 25% reported severe or overwhelming pain (in a questionnaire that classified symptoms as mild, moderate, intense, or overwhelming). Although a different evaluation method has been used (mild, moderate, or severe pain), similarly, this study found a greater presence of severe pain, with 42.53% (question five of the BPI - Average pain intensity in the last 24 h)¹¹. In another study carried out in Brazil, 70.7% of patients had moderate to severe pain on admission, as in the results of this study (71.27%)¹⁰.

Nociceptive pains are the most frequently found in cancer patients¹², as also pointed out in a study carried out in the Northeast of Brazil (70%)¹⁰. However, the results of such study showed a lower frequency of this type of pain (50.58%).

This difference can be explained by the greater presence of intra-abdominal tumors in this sample.

Neuropathic pain, defined as pain that arises as a direct consequence of an injury or disease that affects the somatosensory system^{3,12}, is less common, however difficult to treat and generally requires a combination of pharmacological and non-pharmacological therapies to be adequately controlled¹³.

In the present study, 50.58% of patients had nociceptive pain (including somatic and visceral types) and 39.08% had neuropathic pain. Only 10.34% had mixed pain. Meanwhile, in another Brazilian study, 70% had nociceptive pain, 17.3% had neuropathic pain and 12.7% had mixed pain¹⁰. Therefore, as this study shows a greater presence of neuropathic pain than that found in the literature, the results obtained may be different, since, as already mentioned, this type of pain is more complex to treat than nociceptive pain.

Two estimates of the prevalence of neuropathic pain were observed when comparing different study methods. One based on a systematic review of the literature (32.4% of cancer patients with pain in prospective observational studies in palliative care units) and another on a survey of a group of Italian doctors specializing in palliative care (44.2%). A possible explanation for this discrepancy could be the fact that the Italian centers involved in the research were preferably hospices and home care programs that care for advanced disease patients, high disease burden and greater potential for somatosensory involvement¹⁴.

Combining the two prevalence estimates mentioned above, the authors state that around a third of cancer patients with pain suffer from neuropathic pain¹⁴. This is what was observed in the present study, which assessed patients admitted to an oncology palliative care unit and found neuropathic pain in 39.08% of patients. The fact that the unit's professionals are more adept at diagnosing this type of pain may explain this finding.

Considering that some drugs have multiple indications in palliative care, such as corticosteroids, that are also prescribed for fatigue, hyporexia, tumor edema and neuroleptics for delirium and nausea, the analysis of the use of adjuvants in pain control was hampered in this study. To minimize this effect, we decided to exclude Haloperidol and Dexamethasone from the group of adjuvant drugs.

This study had some limitations that should be taken into account. The sample size was lower than expected due to the exclusion of patients and follow up losses. Moreover, the COVID-19 pandemic contributed to the difficulty in recruiting patients, as it modified hospitalization flows, with isolation of entire wards or floors. The low level of education of the study population may have hindered the applicability of the questionnaires, since many patients had trouble understanding some questions, which was a limitation of the method itself (BPI questionnaire).

Despite the methodological differences, this study brought similar results to others in the literature, showing that, in the population of advanced cancer patients, neuropathic pain has a lower frequency than nociceptive pain, although it is still significant, and deserves to be highlighted due to the difficulty of managing it properly.

Despite the study's limitations, it was possible to observe that the use of adjuvants seems to be associated with better pain control. However, it was not possible to significantly highlight the importance of adjuvants in controlling neuropathic pain, as expected. A larger sample group would be needed to assess this correlation.

As symptom control is one of the principles of palliative care, impeccable pain control is an essential duty for health teams dealing with this profile of cancer patients. Discussing this issue and training the teams are key to improving pain control in these patients.

CONCLUSION

Relatively swift and effective pain control in advanced cancer patients admitted to a specialized palliative care unit

seems to be associated with opioid dose adjustment and the addition of adjuvant drugs. Based on the experience of this unit, the inclusion of adjuvants in pain management in people with cancer should always be considered.

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