
ORIGINAL MANUSCRIPT

Pain Intensity as Prognostic Factor in Cancer Pain Management

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■ Abstract

Aim: The aim of this study was to prospectively assess the prognostic value of initial pain intensity and its duration in advanced cancer patients.

Methods: A prospective study was conducted in a sample of patients with cancer requiring pain control. Patients underwent standard analgesic strategies used in our palliative care units. Pain intensity was measured at admission (T0) and after successful dose titration or opioid/route switching within a week (Ts). Patients were also asked about their pain intensity reported 15 days before admission (T-15). Doses of opioids and duration of opioid use were recorded.

Patients were also assessed for the presence of incident pain, neuropathic pain, alcoholism, delirium, and symptom intensity, including items representing psychological distress. One week after or at time of stabilization (Ts), the opioid response was clinically graded as follows: (1) good pain control; (2) adequate pain control requiring more aggressive

opioid escalation; (3) adequate pain control associated with the occurrence of adverse effects; (4) incapacity to achieve pain control within a week. Opioid escalation indexes and days for dose finding were also recorded.

Results: Pain intensity at T0 and at T-15, opioid doses, duration of opioid therapy, and age were associated with more complex analgesic therapies, which were effective in almost all patients within a week.

Conclusion: High levels of pain intensity, often due to previous undertreatment, are predictive of more complex analgesic treatment. Opioid tolerance, as well as younger age, may also play a role. ■

Key Words: cancer pain, assessment tools, opioid response, pain assessment, pain measurement, opioid, cancer, opioid analgesics, pain intensity, prognostic factors

INTRODUCTION

The heterogeneity and complexity of patients with cancer pain represent a relevant challenge for researchers. The possibility of grouping patients to predict their analgesic response, possibly identifying patients with cancer who are less likely to respond to standard treatment, is of paramount importance.¹ The Edmonton Staging System (ESS) is prognostic tool, which has been designed to enable researchers to speak a common

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Submitted: May 27, 2014; Revision accepted: September 1, 2014
DOI: 10.1111/papr.12259

language and to make meaningful generalization from data of clinical trials. Subsequent versions of ESS (revised ESS, rESS) have been proposed with the intent to select patients with less problematic pain features, requiring a shorter time to achieve stable pain control and less complicated analgesic regimens.²

Several factors, such as neuropathic pain, incident pain, psychological distress, or higher pain intensity, have been identified to influence pain outcomes.³ From a re-analysis of an observational study, a large number of domains were identified, explaining only 16 to 24% of the variability of the pain outcome.⁴ In particular, initial pain intensity was found to be a strong predictor of pain outcome, confirming data from a previous secondary analysis.⁵ A high level of pain intensity “per se”, however, does not seem to be clinically an intrinsic factor, as it may possibly depend on several factors. For example, it may result from a previous undertreatment, which could be potentially resolved in a simple way and could not influence the prognosis.⁶ The multicenter nature of the study, with unselected settings using different procedures of opioid titration and no clear definition of some variables, could have influenced the data. For instance, original data suggested a delayed recourse to strong opioids in a substantial percentage of patients.⁷ Thus, unplanned or nonhomogeneous methods of pain management may explain these findings. In fact, in these studies, several days were needed to reach relatively low doses of opioids despite low levels of pain intensity. For example, patients with moderate–severe pain achieved stable pain control after 8 to 22 days, with doses of 48 to 72 mg of oral morphine equivalents.⁵ Using more intensive protocols in specialist palliative care settings, the achievement of adequate pain control is commonly obtained within 24 to 48 hours, independently of the initial pain intensity.^{8–12} These observations suggest that a timelier opioid titration performed in a specialistic setting can produce a rapid pain control, minimizing the potential influence of initial pain intensity. Rather, a previous undertreatment could be relevant for pain outcome. Moreover, the inclusion of patients with mild pain who are commonly not deemed of changes in analgesic treatment may influence the outcome. Therefore, the analysis should be performed in patients who require some modification of the analgesic treatment, particularly in patients with moderate–severe pain.

The aim of this study was to prospectively assess the influence of initial pain intensity and its duration in a sample of patients who required changes in analgesic

treatment to control pain, according to a similar protocol of opioid dose titration. The secondary outcomes were to re-analyze the principal prognostic factors assessed in literature using specific tools, as well as the previous opioid therapy, in terms of doses and duration.

PATIENTS AND METHODS

Study Design

This prospective study was conducted in a sample of consecutive patients admitted to 2 acute pain relief and supportive care units during an 18-month period. The ethical committee of University of Palermo, Italy, approved the study. All patients provided their informed consent.

Patients

Inclusion criteria were adults; a diagnosis of chronic cancer pain of moderate–severe intensity (> 4 on a numerical scale 0–10); and receiving an analgesic pharmacological treatment, which was unsuccessful at controlling their pain.¹³ Exclusion criteria were an expected short survival (< 1 month), and severe cognitive impairment limiting the assessment.

Procedures

Consenting patients who met inclusion criteria were assessed. At admission (T0), the average pain intensity reported in the past 24 hours was measured using a numerical scale choosing a number from 0 (no pain) to 10 (the worst pain imaginable). Patients were also asked to recall their pain intensity about 15 days before admission (T-15), the amount of analgesic used, and how long they were using opioids at doses of oral morphine dose equivalents ≥ 60 mg/day. Patients were treated with opioids to balance analgesia and adverse effects, eventually supported by symptomatic drugs, according to department policy and routine protocols in the units, previously reported in other studies.¹⁰ Briefly, opioid treatment was individualized according to previous exposure and response, and tailored opioid titration was performed with daily visits, according to the pain intensity and patients’ needs. Changes of route of administration were eventually performed according to the needs, such as patients with nausea and vomiting, which precluded the oral route. When adverse effects

predominated despite supportive treatment, an opioid switching was performed, using starting conversion ratios previously described.¹⁴ Doses were subsequently changed according to the clinical response. Opioid dose stabilization (Ts) was considered the planned daily dose that provided acceptable background analgesia ($\leq 4/10$), with no more than 3 rescue doses as needed, and acceptable adverse effect intensity. Data were expressed in oral morphine equivalents.

Efficacy Measures

Patients were assessed for a series of variables. Principal factors examined for opioid response included pain at admission (T0), 15 days before admission (T-15), and at time of stabilization (Ts) were the. Other factors were also taken into consideration. The presence of breakthrough pain was defined as an episode of severe pain intensity, well distinguished from background pain (at least 3 different points on a numerical scale 0-10). Patients with an incident component due to movement were specifically assessed. The presence of neuropathic component was assessed by PainDETECT,¹⁵ which has been found to have good discriminant validity in patients with cancer.^{16,17} Delirium was assessed by Confusion Assessment Method (CAM),¹⁸ and alcoholism was assessed by CAGE questionnaire (cut-down, annoyed, guilty, eye-opener).¹⁹ Symptom intensity was assessed using the Edmonton Symptom Assessment System (ESAS), which also includes 2 items representing psychological distress.¹²

Opioid Response

One week after starting treatment or at time of stabilization (Ts), the opioid response was clinically graded as follows: (1) good pain control (≤ 4 on a numerical scale 0-10) with minimal opioid escalation and without relevant adverse effects; (2) adequate pain control requiring more aggressive opioid escalation, for example, doubling the doses in 4 days; (3) adequate pain control associated with the occurrence of adverse effects, requiring aggressive symptomatic treatment or eventually opioid/route switching; (4) incapacity to achieve an pain control or prevalence of adverse effects within a week.⁹ The opioid escalation index (OEI) was calculated as a percentage from the initial dose at T0 to T1 (after 1 week), according to the following formula: $OEI\% = [(x-y)/x]/days \times 100$, where x is dose at stabilization, and y is the dose at

admission. OEI in mg was calculated with the following formula: $(x-y)/days$, as oral morphine equivalents.²⁰ The number of days needed to find the effective dose was also recorded.

Statistical Analysis

Statistical analysis of quantitative and qualitative data, including descriptive statistics, was performed for all items. Frequency analysis was performed with chi-square test or Fisher's exact test, as needed for categorical variables. The paired Wilcoxon signed-rank test and paired samples Student's *t*-test were used to compare symptom intensity and opioid dosage, respectively, at the different intervals. The one-way analysis of variance (ANOVA) and Kruskal-Wallis test were used for parametric and nonparametric analysis, respectively, to evaluate differences between the groups. Spearman's rho analysis was used to test for a correlation between pain intensity at different intervals. Multinomial logistic regression analysis examined the correlation between different pain outcome (dependent variable) and various patient characteristics. Data were analyzed by the Epi Info software (version 6.0; Centers for Disease Control and Prevention, Atlanta, GA, U.S.A.) and IBM SPSS Software 21.0 version (SPSS, Inc., Chicago, IL, U.S.A.). All *P*-values were two-sided, and *P*-values < 0.05 were considered statistically significant.

RESULTS

The characteristics of patients are described in Table 1. Data from 8 patients were incomplete or unavailable (Figure 1). Data with outcomes were available in 166 of 174 patients having a pain intensity of $> 4/10$ at T0. The mean age was 65.1 year (SD 11.9), and 70 patients were

Table 1. Characteristics of Patients and Categories of Response

	a	b	c	d
Age (mean and SD)	69.8 (11.6)	65.8 (12.0)	62.3 (11.6)	68.7 (3.8)
Gender (M/F)	17/27	14/21	38/46	1/2
Primary tumor				
Lung	7	6	23	1
Breast	9	9	13	0
Urogenital	9	4	15	2
Gastrointestinal	4	7	7	0
Pancreas	4	3	6	0
Head and neck	3	1	4	0
Others	8	5	16	0

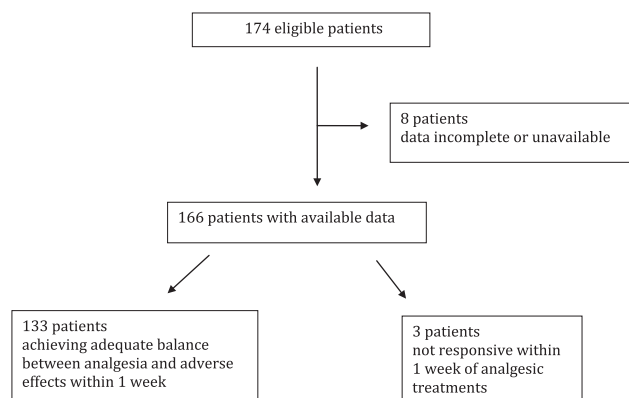


Figure 1. Flow diagram of patients included in the study.

males. The primary diagnoses were in a rank order: lung (n. 37), breast (n. 31), urogenital (n. 30), gastrointestinal (n. 18), pancreas (n. 13), head & neck (n. 8), myeloma (n. 7), liver (n. 5), other (n. 17). One hundred and seven patients (64%) had an incident bone pain, 12 patients (7.2%) had a positive CAGE, and 11 patients (6.6%) had a positive CAM. Twenty-one (12.7%) patients had values of PainDETECT of > 18 (neuropathic component is likely). The mean pain-DETECT value for all patients was 8.9 (SD 7.6).

Table 2 reports pain intensity data and opioid doses at admission (T0), at T-15, and at time of stabilization after opioid titration (Ts). At T-15 and T0, the mean pain intensities were 6.3 (SD 1.5) and 6.7 (SD 1.2), respectively. There was a close correlation between the mean pain intensity at T-15 and at T0 ($P < 0.0005$; Spearman's rho correlation test). Forty-four, 35, and 84 patients had a response "a", "b", and "c", respectively. Most of the patients in category "c" (80 patients, 95%) underwent an opioid switching.

Age predicted the analgesic response (worse in younger patients (age < 65 years), $P = 0.003$), while

Table 2. Number of Patients with Positive CAGE, Positive CAM, Positive Pain-DETECT, Incident Pain, Psychological Distress, Pain Intensity > 7/10 at T0 and T-15, and OEImg > 5, in the Different Categories of Response ("a", "b", and "c")

	a	b	c	P
CAGE positive	4	1	7	0.509
CAM positive	2	2	7	0.693
PAIN DETECT positive(> 18)	7	3	11	0.624
Incident pain	26	25	53	0.516
Psychological distress > 10	10	5	14	0.577
Pain intensity T0 > 7	4	10	29	0.008
Pain intensity -15 > 7	3	10	21	0.020
OEImg >5	11	21	35	0.004

gender did not influence the response ($P = 0.735$). A severe pain intensity ($\geq 7/10$), at T0 and at T-15, and an OEImg > 5 were more often reported in category c ($P = 0.008, 0.020, 0.004$, respectively) (Table 2). In the analysis of frequency and continuous variables, CAGE, CAM, pain-DETECT, incident pain, and psychological distress were not different in the different categories of response (Tables 2 and 4). Changes in ESAS items are reported in Table 3. All the values of ESAS items statistically improved 1 week after the treatment ($P < 0.0005$). The mean OEI% and OEImg were 18.8 (SD 51.6) and 2.3 (SD 20.8), respectively. Pain intensity at T0, but not at T-15, was correlated with response categories ($P = 0.05$ and $P = 0.07$, respectively). There was a significant relation between duration of opioid therapy with ≥ 60 mg oral morphine equivalents before admission and categories of pain response ($P = 0.001$) (Table 4).

Multinomial logistic regression analysis is shown in Table 5. Both pain intensity or pain intensity $\geq 7/10$, at either T0 or T-15, were correlated with the need of more complex treatments (category c). Age (< 65 years), duration of opioid therapy at doses ≥ 60 mg of oral morphine equivalents, doses of oral morphine equiva-

Table 3. Symptoms Recorded with ESAS, OEI%, OEImg, and Oral Morphine Equivalents at T0 and Ts (See Text)

	T0	Ts	P
Pain intensity	6.7 (1.2)	2.2 (0.9)	< 0.0005
Weakness	5.2 (2.4)	4.0 (2.2)	< 0.0005
Nausea	1.5 (2.1)	0.5 (1.3)	< 0.0005
Appetite	4.0 (2.8)	3.1 (2.5)	< 0.0005
Anxiety	3.4 (2.4)	2.4 (2.0)	< 0.0005
Depression	3.3 (2.5)	2.5 (2.3)	< 0.0005
Drowsiness	1.7 (2.2)	1.2 (1.7)	0.005
Dyspnea	0.8 (1.5)	0.5 (1.1)	< 0.0005
Well-being	5.5 (1.7)	4.3 (1.6)	< 0.0005
Total ESAS	27.1 (9.0)	20.5 (9.8)	< 0.0005
OEI%	–	18.8 (51.6)	
OEImg	–	2.3 (20.8)	
Oral morphine equivalents	121 (173)	136 (130)	0.164

Table 4. Continuous Variables for Categories of Response (Univariate Analysis of Variance – ANOVA Test)

	Outcome
Pain DETECT	$P = 0.707$
CAGE	$P = 0.727$
Pain intensity at T0	$P = 0.05$
Psychological distress	$P = 0.498$
Mean Pain intensity -15	$P = 0.070$
Duration opioid therapy	$P = 0.001$

Table 5. Multinomial Logistic Regression Analysis

Parameter	Multinomial Logistic Regression		
	Exp(B)	95% CI	P
Mean pain intensity a T0	1.45	1.01 to 2.10	0.05*
	1.38	1.02 to 1.86	0.035 [†]
Pain intensity ≥ 7 a T0	4.0	1.13 to 14.13	0.031*
	5.3	1.71 to 16.19	0.004 [†]
Mean pain intensity a -15	1.46	1.05 to 2.03	0.025*
	1.18	0.92 to 1.51	0.202
Pain intensity ≥ 7 a -15	5.6	1.38 to 22.21	0.015*
	4.9	1.37 to 17.58	0.014 [†]
Age	0.97	0.93 to 1.0	0.127
	0.94	0.91 to 0.98	0.001 [†]
Duration of opioid therapy (> 60 mg/day of oral morphine equivalents)	0.87	0.59 to 1.28	0.479
	1.63	1.23 to 2.16	0.001 [†]
Oral morphine equivalents T0	0.99	0.98 to 0.99	0.020*
	1.0	1.01 to 1.02	0.020 [†]
Days of dose finding	1.49	1.03 to 2.17	0.033*
	2.24	1.59 to 3.15	< 0.0005 [†]
OEImg > 5	5.09	1.89 to 13.64	0.001*
	2.12	0.94 to 4.77	0.069
OEI%	1.03	0.99 to 1.05	0.059
	1.01	0.98 to 1.03	0.334

*“a” vs. “b” category.

[†]“a” vs. “c” category.

lents at T0, OEImg > 5, as well as days for dose finding, were associated with more complex treatments.

Only 3 patients (1.8%) had a response “d” (poor pain control/prevalent adverse effects) after 1 week of treatment and were not considered for statistical purposes. These patients had a mean pain intensity at T0 and T-15 of 7.7 (SD 0.6) and 7.5 (SD 0.7), respectively, and an OEImg of 32.4 (SD 31.4) and OEI% of 11.3 (SD 0.14), respectively. Two patients had a pain intensity ≥ 7/10 at T0. All patients had incident pain and pain intensity at T-15 ≥ 7/10.

DISCUSSION

The principal finding of this study was that pain intensity recorded at time of admission influences the analgesic response to a timely and standardized analgesic treatment. The efficacy of the analgesic treatment is evidenced by the improvement of pain intensity and symptoms, as recorded by the changes in ESAS. In fact, almost all patients (163/166, 98.1%) achieved adequate pain control with acceptable opioid-related symptoms within 1 week.

However, we also observed that there was a correlation between pain at T0 and pain at T-15 and categories of response, confirming that patients with prolonged uncontrolled pain are likely to need more complex treatments such as aggressive symptomatic

therapies and opioid/route switching, although not necessarily a bad prognosis. In fact, most patients achieved an acceptable analgesia within 1 week with an appropriate and timely use of opioids.

In a secondary analysis of prospectively collected data from a multicenter study for classifying advanced cancer patients with pain, the initial pain intensity has been indicated as a contributing factor in requiring a longer time to achieve stable pain control, high final opioid doses, and more complicated analgesic regimes.⁵

In a subsequent multicenter study of unselected patients referred to palliative care, pain intensity was independently associated with pain prognosis, in terms of days to achieve stable pain control.³ In a further secondary analysis of data of an epidemiological study on the pattern and quality of cancer pain management, pain intensity was found to predict pain outcome after 2 weeks.⁴ Original data from these studies, however, showed that undertreatment in the longitudinal part of the study strongly biased the outcome, as treatments were nonstandardized and probably nonoptimized.⁷ The method of titration and consequently the median length of time to achieve stable pain control in patients with moderate–severe pain required a median of 8 to 22 days, with small dose increments of opioids.⁵ The initial pain intensity is a relative concept, as it depends on the time the patient is intercepted in its trajectory along the course of disease.²¹ Indeed, several surveys and also daily practice in experienced palliative care centers suggest that pain control is obtained in a few days in most patients using an adequate opioid dose titration.^{8,9,11} Thus, one could argue that different settings could have used different procedures of opioid titration, or that no established protocol was planned in multicenter studies performed in different centers. In a secondary analysis of patients treated with similar protocols, initial pain intensity did not predict the outcome after an appropriate opioid titration.¹⁰

Our hypothesis was that pain intensity at time of examination cannot be considered “per se” as a well-defined factor predictive of a poor analgesic response, along the course of pain trajectory, as it depends on referral characteristics, for example, treatment behavior on behalf of previous teams or GPs, rather than on pain/patient characteristics. Alternately, the level of opioid tolerance may play a role. The reasons rely on the clinical experience of patients who are often undertreated at referral (they present high pain intensity and receive inadequate therapy). They then respond to adequate changes of therapy, in some case, just minimal increases

in opioid doses. Thus, a poor analgesia may result from a development of tolerance or a progression of disease unbalanced by timely changes of the treatment.

We designed the study to ascertain the role of lasting undertreatment or poor analgesia at time of admission to palliative care units. Moreover, we restricted the selection of patients to a group with a level of pain requiring changes in analgesic treatment, commonly based on moderate–sever pain ($> 4/10$). The presence of a group of patients, who would not change the treatment because they already have well controlled pain, could interfere with the outcome, often based on the time needed to find a good balance between analgesia and adverse effects.^{3,5} We also considered 1 week as an acceptable cut-off for opioid titration or changes in pain management.^{8,10,11} This finding was confirmed even stratifying the patients according to the level of pain intensity: patients with severe pain intensity ($\geq 7/10$) at T-15 and T0 more frequently required aggressive symptomatic treatment or opioid/route switching than patients with moderate pain. This finding is consistent with the observation that patients with severe pain are likely to be admitted within 30 days.²²

Younger patients (< 65 y) most frequently required complex therapies. This finding confirms previous observations.^{3,4} As expected, OEI was related with the categories of response. This score, however, should not be considered as a prognostic factor but as a means to evaluate the analgesic response.^{20,23} Of interest, the doses of opioids used at T0 were correlated to the analgesic response. In pioneer studies, the level of tolerance was initially considered to be a predictive factor.¹ This factor has been removed from subsequent pain classification systems.²⁴ Instead, it is likely that when eliminating the range of patients with mild pain or no pain, the duration of treatment with ≥ 60 mg of oral morphine equivalents may influence the outcome of patients with moderate–severe pain intensity. Similarly, patients receiving higher doses of oral morphine equivalents may require more aggressive pharmacological treatments more often. Patients who have been treated with higher doses opioids or for prolonged periods of time may require further dose escalation, possibly producing adverse effects and the need of opioid switching. It has been found that integrated outcome of pain score and opioid consumption may provide a mean for integrated analgesic assessment.²⁵ This issue deserves further investigation.

Other aspects regarding previous factors taken into consideration for the pain outcome have been consid-

ered. The poor correlation between other factors, such as CAGE, CAM, neuropathic pain, and incident pain, commonly included in the analysis of pain prognosis, and pain response reported in this study, is explainable by the low number of patients having the predictive factors taken into consideration. Despite a higher number of patients with positive CAGE, CAM, painDETECT, psychological distress, measured with 2 specific items of ESAS, and incident pain were found in category “c”, this data did not attain statistical significance. Moreover, the selection of patients having poor pain control at time of initial evaluation possibly flattened the data. In fact, patients with adequate pain control were not included in the study, as they do not require further refinements of the analgesic therapy. Finally, patients with uncontrolled pain had clearly distinguishable superimposed pain, explaining the figures regarding breakthrough pain, and, specifically, incident pain due to movement. In fact, almost all patients presented episodes of breakthrough pain. Although this should not be exactly considered according to basic definition, it has been reported that patients with uncontrolled pain are more likely to develop breakthrough pain.²⁶

This article may have some limitations. Patients were recruited in 2 palliative care units and the findings cannot be extended to other settings. These units have been sharing protocols and research projects for many years. Treatments are quite homogeneous and not significantly variable between treating physicians. The homogeneity of treatments providing an adequate pain control in most cases in a few days should be considered as a standard of any specialistic palliative care setting. This approach may provide a better guarantee regarding the data, as multicenter studies with large number of patients but different modalities of intervention, may more often provide less reliable data.²⁷

The second aspect regards the recall of pain intensity 15 days before admission. However, there is no way to intercept a patient before the admission, unless selecting patients and leaving them without allowing an analgesic intervention. From the practical and ethical point of view, this would have been quite problematic. Moreover, in patients with cancer pain, recall ratings have been found to be reliable as outcome measures in clinical trials.²⁸

Finally, the number of patients who were considered unresponsive after an intensive treatment of 1 week (category “d”) was quite low to extrapolate useful information. Thus, the risk factors individualized in this study regard patients requiring more complex

treatments (category c), but not necessarily those who have a negative prognosis. A more aggressive treatment with opioids in an appropriate setting, including strict assessment and monitoring while titrating opioid doses, or changing opioid or route of administration, may significantly improve the opioid response. Meaning, regardless of possible interfering factors, almost all patients with cancer may achieve a good balance of analgesia and adverse effects with an appropriate analgesic treatment in a specialized setting of palliative care.²⁹

In conclusion, the level pain intensity at admission requires a more aggressive treatment for patients with cancer with moderate–severe pain intensity who require changes in analgesic treatment. This level of pain intensity is long lasting due to a previous undertreatment, as it is related to level of pain intensity recalled 15 days before. Similarly, opioid doses, duration of opioid therapy, and younger age may require more aggressive treatment. In this group of patients, other factors previously reported to influence the outcome seem to have less importance, possibly because the lack of a comparator group with mild pain. However, this level of pain does not usually require changes in analgesic treatment and cannot be discriminative.

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