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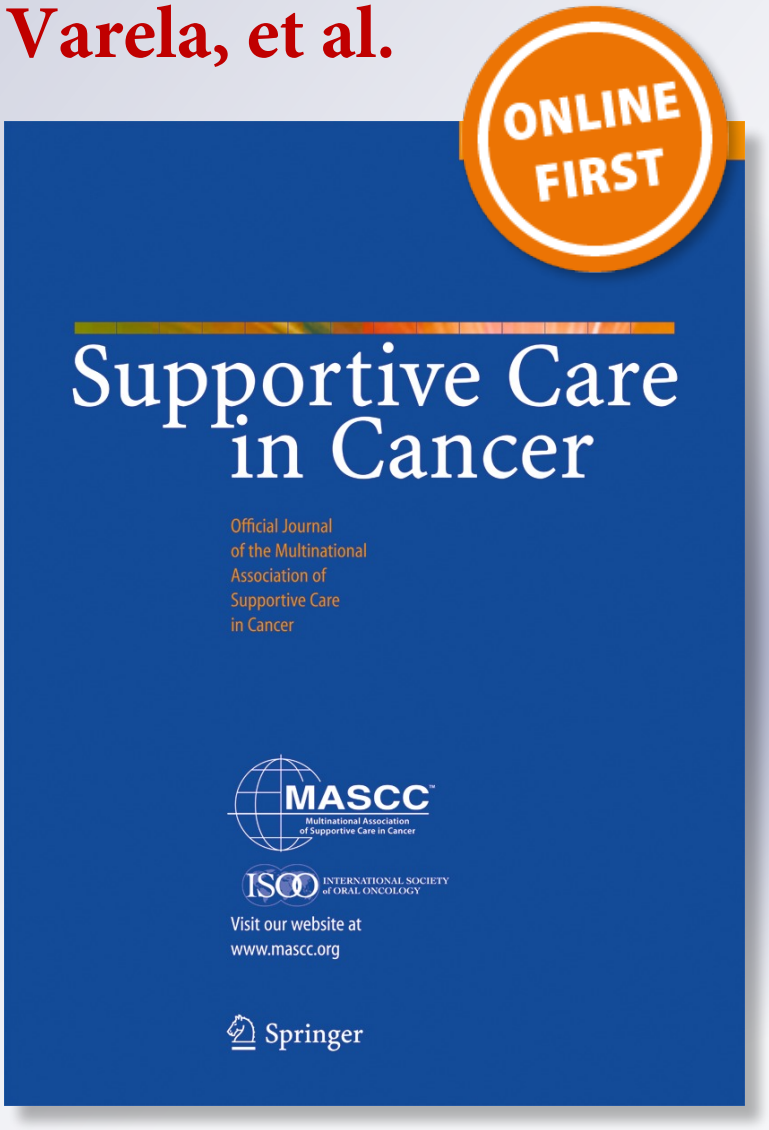

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ORIGINAL ARTICLE

Methadone as first-line opioid treatment for cancer pain in a developing country palliative care unit

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Abstract
Purpose The use of methadone for cancer pain is limited by the need of expertise and close titration due to variable half-life. Yet, it is a helpful palliative strategy in low-resources countries given its long-acting effect at low cost and worth additional study. Our aim was to describe the prescription and outcomes of methadone as a first-line treatment for cancer pain in a tertiary palliative care unit (PCU) in Argentina.
Methods Retrospective review of medical records of patients with moderate to severe cancer pain seen at the PCU in 1-year period, who initiated strong opioids at the first consultation. Data collected during the first month of treatment included disease and pain characteristics, initial and final opioid type and dose and need for opioid rotation.
Results Methadone was the most frequent opioid both at the initial and last assessment (71 and 66 % of the prescriptions). In all, treatment with strong opioids provided considerable decrease in pain intensity ($p < 0.001$) with low and stable opioid dose. Median and interquartile range (IR) of oral morphine equivalent daily dose (OMEDD) was 26 (16–32) and 39 (32–55) mg for initial and final assessments, respectively ($p = 0.3$). In patients initiated with methadone, the median (IR) daily methadone dose was 5 (4–6) mg at first and 7.5 (6–10) mg at final assessment, and the median (IR) index of opioid escalation was 0 (0–4) mg; ($p < 0.05$). Patients on methadone underwent less percentage of opioid rotation (15 versus 50 %; $p < 0.001$) and longer time to rotation (20.6 ± 4.4 versus 9.0 ± 2.7 days; $p < 0.001$) than patients on other opioids.
Conclusions Results indicate the preference of methadone as first-line strong opioid treatment in a PCU, providing good pain relief at low doses with low need for rotation. Several considerations about the costs of strong opioids in the region are given.

Keywords Cancer pain · Methadone · First-line strong opioid · Developing countries

Introduction

The multidimensional treatment of pain constitutes one of the main goals of palliative care (PC) in patients with advanced cancer. The use of strong opioids is an essential tool to manage moderate to severe cancer- related (CR) pain [1, 2, 3]. However, in many low-income regions, the high restrictive prices of opioids determine elevated rates of under treatment [4, 5, 6]. An extensive study all over the world determined that morphine, the main first-line strong opioid recommended in the cancer pain guidelines, is often unaffordable [7]. In 1996, Watanabe suggested the usefulness of methadone as an effective and inexpensive alternative [8]. In effect, the synthetic opioid methadone was found to be less expensive than morphine in most countries, constituting the most cost-effective, long-acting strong opioid, [6, 7] and a suitable alternative to morphine for developing countries. A double-blind study

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showed that morphine and methadone provided comparable analgesia and overall tolerability [9]. In addition, methadone shows excellent absorption and does not have any known active metabolites [10, 11] and was shown to induce low opioid tolerance [10, 11] and to be highly effective for neuropathic pain [12]. Unfortunately, its long and unpredictable half-life and the potential of drug accumulation and delayed toxicity require careful initiation and titration schedules, limiting its use and the generation of evidence-based recommendation [10, 11, 13]. Larger specific data from the region regarding the modality and outcomes of the use of methadone is needed to ease its access by physicians and patients.

Many distinctive characteristics of our work at a comprehensive third level palliative care unit (PCU) in a public hospital in Argentina, including profound clinical skills of the professionals and a close follow-up of our patients with 24 h-available contact, together with the versatility of routes of administration (oral, rectal, or sublingual) and the small number and high cost of other long-acting opioids in our community, have determined high rates of methadone use in our daily practice during the last years. The objective of the present study was to retrospectively and systematically document the use and outcomes of methadone among other strong opioids, as the initial choice for the treatment of moderate to severe CR pain during the first month of treatment in our PCU.

Methods

Study design and setting

In this retrospective study, data referred to the first month of treatment of all new patients with severe or moderate CR pain, referred to a tertiary PCU between July 2012 and June 2013, was collected from the medical records. The study comprised inpatients from the general institution's wards and inpatient and outpatients from the PCU services, who received multidisciplinary care led by the PC team. Inpatients were routinely followed up daily whereas outpatients were seen a variable number of times depending on their needs. A telephone medical ward was available 24 h/day; additionally, a phone call to the outpatient or family was regularly performed 48 h after consultation to evaluate the treatment response. Procedures followed in this study were in accordance with the ethical standards of the Institutional Review Boards and the Helsinki Declaration [14].

Participants and inclusion criteria

All adult strong opioid-naive patients who underwent an initial consult to the PCU professionals for the treatment of moderate to severe cancer pain, and who initiated strong opioids at the first consultation, were included.

Data and measures

Baseline demographic and medical data regarding age, sex, diagnosis, disease status, and Eastern Cooperative Oncology Group (ECOG) performance status was obtained at the first visit. Initial pain was classified as nociceptive, neuropathic, or mixed. Self-perceived severity of pain was assessed through ordinal scales as severe, moderate, or mild. Predictors of poor prognosis for achieving pain relief were assessed through the Edmonton Staging System (ESS) [15]. For each patient, the initial and final prescribed opioid, the opioid dose in milligram per day and in oral morphine equivalents daily dose (OMEDD) [16, 17], as well as the pain intensity, were assessed. In those patients who were prescribed methadone as first-line opioid, the opioid escalation index (OEI) in milligram was calculated according to the following formula: OIE = (final dose – initial dose)/days of treatment [18]. Other variables were adverse effects and frequency and reasons for opioid rotation (OR).

Data analysis

Descriptive statistical analysis was conducted. Media ± standard deviation (SD) or median and interquartile range (IR) was obtained. Differences between continuous variables were analyzed by Student's t test (normal distributed data) or Wilcoxon tests (non-normally distributed data). Relationship between discrete variables was tested using Pearson's chi-squared test (χ^2) test. $P < 0.05$ was considered significant. Data were collected and analyzed using appropriate software.

Results

Participants

Data collection flow chart of patients is shown in Fig. 1. Of a total of 136 patients with CR pain referred to the PCU in the study period, 16 were excluded because they had previously been exposed to strong opioids. Of the remaining 120 patients, 77 (64.2 %) were prescribed strong opioids at the first consultation. A total of 56 (72.7 %) medical charts were recovered from the central registry and included in the analysis.

Forty-two patients (75 %) attended more than one consultation. The remaining 14 patients had only one consultation due to different causes, as referral to other team, second consultation after 1 month, loss of follow-up, or death.

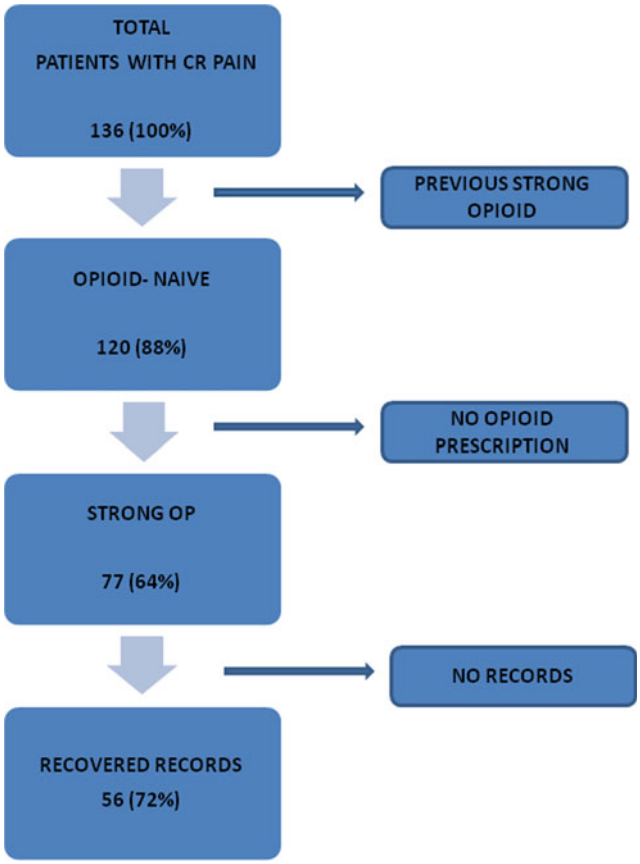

Fig. 1 Flow diagram of participants in the study

Baseline measures

Patients clinical and demographic information at baseline is summarized in Table 1. The mean ± SD age was 64.6 ± 7.2. Most of the patients were men; 73 % had advanced cancer being the most frequent primary site gastrointestinal, and more than half exhibited ECOG score 3–4. Most (58.9 %) were outpatients at the time of the first consultation. Baseline characteristics of pain are shown in Table 2. There were similar proportion of patients with moderate and severe pain. Among those patients in which the nature of pain was registered, 49.2 % reported neuropathic or mixed pain and 33 % nociceptive pain. Poor prognosis factors were detected by ESS score = 2 in 60.6 % patients.

Opioid treatment

At the moment of the first consultation, 46.5 % of the patients were completely opioid-naive, 46.5 % were receiving weak opioids (23.5 % tramadol, 14 % propoxyphene, 7 % codeine, and 2 % meperidine), and in the rest 7 % no data (ND) was found. The previous weak opioid was completely stopped at the day of strong opioid initiation. The percentage of patients assigned to each opioid as well as opioid dose expressed as OMEDD was assessed at the first and last consultations.

Table 1 Demographics and baseline characteristics of patients (n = 56)

	%
Sex	
Male	58.9
Female	41.1
Tumor	
Gastrointestinal	32.1
Lung	26.8
Genitourinary	10.7
Breast	8.9
Gynecological	8.9
Prostate	3.6
Unknown	3.6
Other	5.4
Advanced state disease	74.3
Metastasis	55.4
Loco-regional	18.9
ECOG	
0–2	46.4
3–4	51.8
N/R	1.8
Setting	
Outpatient	58.9
Inpatient	41.1

ECOG Eastern Cooperative Oncology Group Performance Status, *N/R* data not registered

Methadone was the most frequent opioid, either at initial and last assessments, followed by a markedly lower percentage of morphine, oxycodone, and fentanyl **(**Fig. 2**)**. Methadone as first-line opioid was prescribed in 87 % of the outpatients and 47 % of the inpatients. In all patients, the mean follow-up time was 13 ± 7 days, and no significant differences between the initial and final opioid dose expressed as OMEDD

Table 2 Baseline Characteristics of Pain

	% pts
Intensity of pain	46.2
Severe	53.8
Moderate	
Type of pain	49.2
Neuropatic/Mixed	33.3
Nociceptive	17.5
N/R	
ESS	15.7
1	60.6
2	23.7
N/R	

ESS Edmonton Staging System, *N/R* data not registered

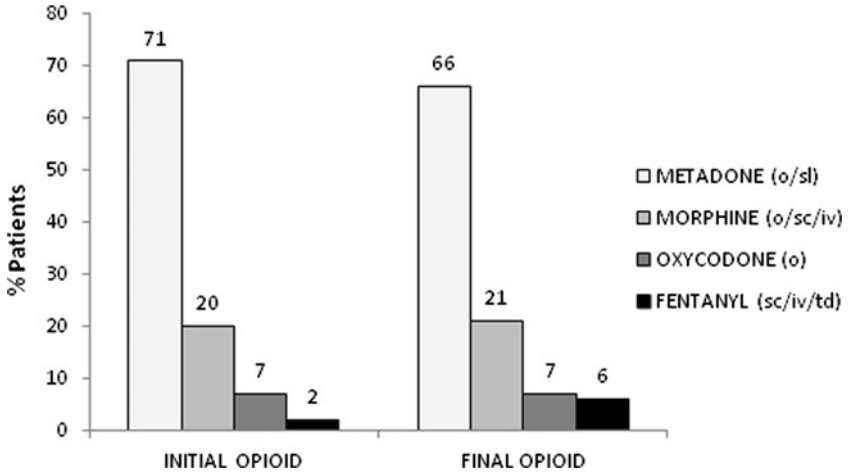

Fig. 2 Prescribed opioid. The percentage of patients assigned to each opioid at initial and last assessments is shown. Routes employed for administration were *o* oral, *sl* sublingual, *sc* subcutaneous, *iv* intravenous, *td* transdermic

were observed [Median (IR) = 26 (16–32) mg, $n = 56$ and 39 (32–55) mg, $n = 42$, respectively; $p = 0.4$]. When considering only those patients who were indicated methadone as first line (71 % of the total), the mean follow-up time was 11 ± 2 days, and there was a statistically significant increase in dose between the initial and final assessments [Median (IR) daily methadone dose = 5 (4–6) mg (n = 40) and 7.5 (6–10) mg (n = 31), respectively ($p \leq 0.05$)], with an opioid escalation index OEI of 0.2 (0.0–0.3) mg.

Overall, 13/56 (23.2 %) patients on strong opioids were switched to another, with a total of 14 OR being conducted. Among the 40 patients who initiated on methadone, 6 (15 %) required OR, whereas 8 of 16 patients (50 %) who initiated on opioids other than methadone required OR ($p < 0.001$, χ^2 Test). In addition, the interval between the first day and OR was 20.6 ± 4.4 days in patients initiated on methadone and 9.0 ± 2.7 days in patients initiated on other opioids ($p < 0.001$, Student's *t* test). Opioid-induced neurotoxicity (OIN) [19] was the most common indication for OR (71.4 %), followed by impairment in the route of administration experienced by 14.3 % of the patients.

Pain intensity

Self-reported pain intensity at the last follow-up was compared with that at baseline in those patients who attended more than one consultation ($n = 42$, Fig. 3). There was a marked decrease in the percentage of patients reporting moderate and severe pain (53.8 to 20.1 % and 46.2 to 11.4 %, respectively; *$p < 0.001$, χ^2 Test) between the first and last assessment, while the proportion of patients with mild or no pain at the first consultation increased from none to 31.4 and 37.1 % at the last assessment, respectively. Similar results were observed for the group of patients initiated with methadone (Fig. 4, n = 31; *: $p \leq 0.01$, χ^2 Test).

Discussion

Pain is one of the most frequent and distressing cancer-related symptoms affecting 70 to 90 % of patients with advanced cancer. Yet, and specially in developing countries, high rates of under-treatment persist, mostly due to drug availability [5, 7] and lack of evidence-based local guidelines. The present study aimed to retrospectively document our experience in the use of first-line methadone among other strong opioids as the most cost-effective, long-acting treatment for moderate to severe CR pain at a tertiary PCU.

We found that methadone was the most frequently prescribed strong opioid both initially and in the final assessments (71 and 66 %). While current literature points out morphine as the mainstay option in patients with pain requiring strong opioids [1, 3], and the rotation to methadone from other opioids has been well documented [20, 21, 22, 23], little has been reported regarding the use of methadone as the first line choice. In a review made in 2002, Bruera et al. [11] concluded that methadone is an important alternative first-line agent for

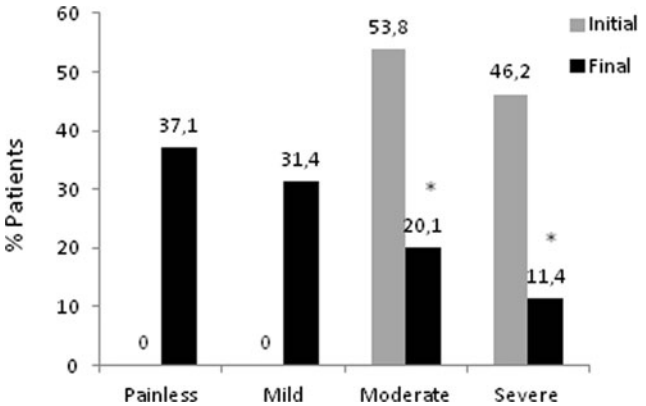

Fig. 3 Variation in pain intensity. Pain intensity at the first and final consultation was assessed in those patients who attended more than one consultation ($n = 42$; *$p < 0.001$, χ^2 test)

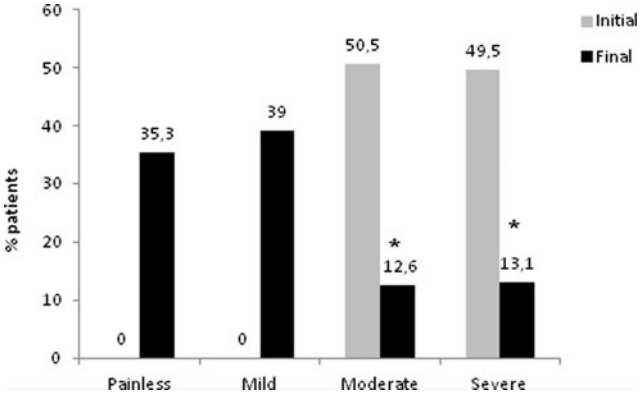

Fig. 4 Variation in pain intensity in patients initiated with methadone. Pain intensity at the first and final consultations was assessed in those patients initiated with methadone who attended more than one consultation ($n = 31$; $^*p < 0.01$, χ^2 test)

CR pain, underlying the need for further research in its use. Afterwards, other studies showed its safety and comparable analgesic efficiency and tolerability than morphine [24, 25], in some cases without generating opioid-induced hyperalgesia [26] and dose escalation [27]. A detailed randomized trial [9] comparing the efficacy of sustained-release morphine 15 mg twice a day versus methadone 7.5 mg twice a day demonstrated that both treatments were similarly effective regarding pain response and tolerability.

In our PCU, patients were initiated on regular methadone 2.5–5 mg twice or three times daily, with additional prescription of rescue methadone. Our results indicate that the overall mean opioid dose along the whole study period remained relatively stable and low and was comparable to the usual initial dose for most strong opioids (MEDD < 50 mg) [1, 3]. When considering the subgroup of patients administered methadone as first line, a statistically significant increase in dose was evidenced between the first and last assessments; however, it is worth to mention that such increase may not be clinically meaningful. Moreover, the final doses of methadone remained low and comparable to initial methadone doses recommended in other previous reports [27, 28], and the median OEI was very low (0.2), since many patients did not underwent dose increase or even underwent dose decrease.

In spite of the small doses, pain intensity in the last consult was significantly lower than values recorded at admission, both with methadone and the other strong opioids. Analysis indicated a marked decrease in self-reported moderate and severe pain, with more than 30 % of the patients reporting no pain at the end of the study. We hypothesize that the multidimensional management of *total* pain [29] aimed to relieve physical, emotional, and spiritual distress, characteristic of a comprehensive PC team intervention, may account for the observed low opioid doses. Alike the study by Parsons et al. [25], we found that methadone as initial strong opioid provided significant pain control at low doses and low necessity of rotation. Moreover, our results also suggest a possible and extensive (87 %) use of methadone in the outpatient setting.

Opioid rotation was performed in 23 % of the cases. Notably, the switches were more than twice less frequent when initiating on methadone than on other opioid, and the mean interval between the primary opioid and rotation was twofold, suggesting that methadone provides a better control of pain in this group. In accordance with the previous systematic and critical review, the main cause for rotation for all the different opioids used herein was OIN [30]. Other common symptoms often requiring OR might have been controlled by prophylactic antiemetic and laxative, which are routinely prescribed to all patients who start opioid treatment at the PCU.

As a side, interesting observation, 27 % of the study population did not had advanced cancer, which can be understood as supporting the trend to integration of PC in earlier stages of the malignant disease.

Like others, our results settle on methadone as a preferable first-line CR pain treatment due to its effectiveness at low cost. In the present work, the cost of the required mean overall opioid daily dose (34.5 mg) resulted twice less expensive for methadone (0.1 USD) than for morphine (0.2 USD), and taking into consideration methadone's higher relative potency, differences in costs would increase at higher doses. Furthermore, methadone results less expensive than other existing rapid- and sustained-release opioid preparations. Comparisons in Argentina show that whereas the cost of 60 mg oral morphine solution per 30 days is 10.55 USD, the cost of equianalgesic doses of oxycodone solution is 16 USD, transdermal fentanyl 242 USD and oral methadone solution 5 USD. At the same dose, methadone solution made by powder is around 25 times less expensive than equianalgesic doses of sustained-release oxycodone (118 USD) and morphine (128 USD) [31]. Methadone long lasting effect supports the rationale for dosing it two/three times, or even once a day, therefore providing a comfort comparable to other opioid sustained-release formulations.

Major limitations of this study are the lack of information regarding individual opioid- and opioid rotation- induced side effects, the undocumented coexistence of onco-specific treatments or other medications, the small population sample, and incomplete documentation, including missing charts.

Despite these limitations, our preliminary results are indicative of the preference of methadone as a first line opioid in the management of CR pain, accounting for more than two-thirds of the indications at the PCU. If we assume that the patients whose charts were missing (21) had not received methadone, the percentage of patients initiating on methadone would have decreased from 71 to 48 % (37/77). This number is still considered a high rate of utilization. In addition, methadone seemed to provide good pain relief with low need of switching to another opioid.

The trends observed in this pilot study will guide the design of a hypothesis-driven prospective study pointing to ascertain methadone efficacy and benefits and clarify reasons for its eligibility, providing useful information for low economic resources countries with limited opioid alternatives.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Disclosures None.

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