REVISTA BRASILEIRA DE ANESTESIOLOGIA

Official Publication of the Brazilian Society of Anesthesiology
www.sba.com.br

SCIENTIFIC ARTICLE

Morphine as first medication for treatment of cancer pain

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Abstract
Background and objectives: the medications used according to the recommendation of the World Health Organization do not promote pain relief in a number of patients with cancer pain. The aim of this study was to evaluate the use of morphine as first medication for the treatment of moderate cancer pain in patients with advanced and/or metastatic disease, as an option to the recommendations of the World Health Organization analgesic ladder.
Method: sixty patients without opioid therapy, with ≥18 years of age, were randomized into two groups. G1 patients received medication according to the analgesic ladder and started treatment with non-opioids in the first, weak opioids in the second, and strong opioids in the third step; G2 patients received morphine as first analgesic medication. The efficacy and tolerability of initial use of morphine were evaluated every two weeks for three months.
Results: the groups were similar with respect to demographic data. There was no significant difference between the groups regarding pain intensity, quality of life, physical capacity, satisfaction with treatment, need for complementation and dose of morphine. In G1 there was a higher incidence of nausea ($p = 0.0088$), drowsiness ($p = 0.0005$), constipation ($p = 0.0071$) and dizziness ($p = 0.0376$) in the second visit and drowsiness ($p = 0.05$) in the third.
Conclusions: the use of morphine as first medication for pain treatment did not promote better analgesic effect than the ladder recommended by World Health Organization, with higher incidence of adverse effects.

Morfina como primeiro medicamento para tratamento da dor de câncer

Resumo
Justificativa e objetivos: Os medicamentos usados segundo a recomendação da Organização Mundial de Saúde (OMS) não promovem alívio da dor de uma parcela dos pacientes com dor oncológica. O objetivo deste estudo foi avaliar o uso de morfina como primeiro medicamento para o tratamento da dor oncológica moderada, em pacientes com doença avançada e/ou metástases, como opção às recomendações da escada analgésica preconizada pela OMS.

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Método: Sessenta pacientes sem terapia com opioide, com idade maior ou igual a 18 anos, foram distribuídos aleatoriamente em dois grupos. Os pacientes do G1 receberam medicamentos segundo a escada analgésica e iniciaram o tratamento com não opioide no primeiro degrau, opioide fraco no segundo e opioide potente no terceiro; os do G2 receberam morfina como primeiro medicamento analgésico. Foram avaliadas a eficácia e a tolerabilidade do uso inicial de morfina, a cada duas semanas durante três meses.

Resultados: Os grupos foram semelhantes quanto aos dados demográficos. Não houve diferença significativa entre os grupos quanto à intensidade da dor, qualidade de vida, capacidade física, satisfação com o tratamento, necessidade de complementação e dose de morfina usada. No G1 houve maior incidência de náusea ($p = 0,0088$), sonolência ($p = 0,0005$), constipação ($p = 0,0071$) e tontura ($p = 0,0376$) na segunda consulta e para sonolência ($p = 0,05$) na terceira.

Conclusões: O uso de morfina como primeiro medicamento para tratamento da dor não promoveu melhor efeito analgésico do que a escada preconizada pela OMS e houve maior incidência de efeitos adversos.

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Introduction

The prevalence of cancer has increased, with an estimated projection for 2020 of 17 million new cases.[1] This means that there will be an increase in individuals with pain caused by the disease and by treatment.[2]

The World Health Organization (WHO) developed the analgesic ladder as a guideline for the treatment of cancer pain and recommended the use of nonsteroid anti-inflammatory drugs (NSAIDs) for mild pain on the first, weak opioids for moderate pain in the second, and potent opioids for severe pain in the third step. Adjuvant drugs may be involved in all steps.

In a retrospective study of 1229 patients with cancer pain, the author reports that the analgesic ladder is effective in 71%.[3] Many patients do not get adequate pain relief.[4,5]

Factors related to patients, healthcare institutions and regulatory policies on drug use contribute to the undertreatment of pain.[6,7] Many patients with moderate to severe pain do not receive analgesics and only 24% of those with severe pain are medicated with a potent opioid. In one study, 32% of patients reported that the discomfort was so great that they preferred death.[8] Despite the evolution of knowledge about pain, more than 80% of patients with advanced cancer suffer from pain.[9] In a systematic review, the authors suggest that pain is undertreated in approximately half of patients.[10]

Few studies have proposed an alternative to the WHO ladder[11] and suggested that opioids are prescribed inappropriately.[12] In a review, the authors suggest that the WHO protocol does not use evidence-based recommendations.[13] Some authors criticize the restriction of potent opioids for the third step.[14] In a study of 5084 patients, 56% had moderate to severe pain at least monthly.[8] Better pain control and patient satisfaction could be obtained with the use of potent opioids as first medication.[14]

Because of these controversies, further studies are needed. The aim of this study was to determine whether the use of morphine in the first step of the WHO ladder can improve the outcome.

Method

Model

Prospective randomized study.

Participants

After approval by the Ethics Committee and the informed written consent was obtained, the effectiveness of morphine used in the first step of the WHO ladder was investigated in patients with locally advanced and/or metastatic cancer. Patients with difficulty in maintaining clinical follow-up, cognitive impairment and previous treatment with opioids were excluded. The study was registered at clinicaltrials.gov under number NCT01541124.

Randomization, intervention and evaluation

The patients were divided into two groups with the use of envelopes containing the number of the patient and the group to which he (she) belonged. Patients were included in the sequence by allotment in the visit. G1 patients were treated according to the guidelines of the WHO analgesic ladder and started on the first step, with paracetamol 1 g every six hours (maximum dose 4 g/day); in the second step, codeine (30 mg) every four hours (maximum dose of 360 mg/day); and morphine 10 mg every four hours in the third step. G2 patients received morphine 10 mg every four hours. Whenever indicated, adjuvant drugs were associated to the treatment.

According to pain intensity, G1 patients switched drug in obedience to the analgesic ladder and G2 patients had adjusted the dose of the analgesic drug. The need for palliative cancer therapy, such as radiotherapy, chemotherapy or hormone therapy, was indicated by the oncologist.

Pain intensity every two weeks by using the visual analogue scale (VAS), quality of life every four weeks through the brief questionnaire of quality of life of the WHO,[15] satisfaction with treatment, physical capacity as assessed by the Eastern Cooperative Oncology Group (ECoG) index,[16] and
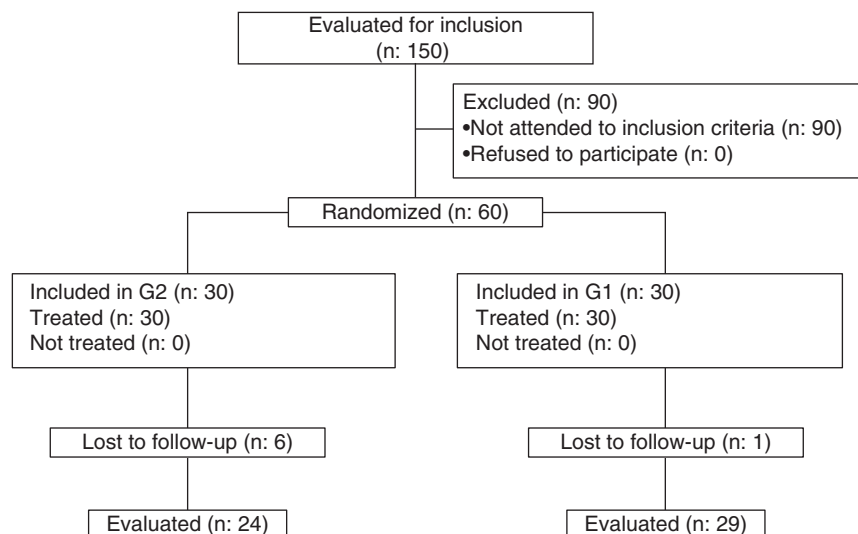
Figure 1 CONSORT diagram.

need for supplemental analgesics were evaluated. Adverse effects were recorded. Follow-up was done for three months or until the death of the patient.

Statistical analysis

To calculate the sample size, BioEstat 2.0 program was used. The mean and standard deviation of another similar study were used as reference.[14] For a confidence level of 95% and a study power of 80%, 30 patients per group (60 in total) were required. For the statistical analysis, GraphPad Prism program was used. The Student t test to compare age, weight and height; chi-square test for patient satisfaction, need for complementation and adverse effects; and Mann–Whitney test for pain intensity, quality of life and physical function were used. p-Values ≤ 0.05 were considered statistically significant and the results were expressed as mean $\pm$ SD.

Results

The sequence of this study is shown in the diagram (Fig. 1). 60 patients were included, 30 in each group. By reason of death, only 24 patients from G1 and 29 from G2 completed the study. The groups were similar with respect to demographics (sex, age, weight and height) (Table 1).

The most common locations of tumors were in the head and neck (G1: 22, G2: 26), with the same region for pain

(G1: 21, G2: 26). The most frequent type of pain was somatic (G1: 27, G2: 30). There was no significant difference between the groups with respect to the pain duration (G1: 4 m; G2: 3 m) and previous use of paracetamol (G1: 5, G2: 2), dipyrone (G1: 24, G2: 24) NSAIDs (G1, 4 G2: 10), tricyclic antidepressants (G1, 1 G2, 1), anxiolytics (G1: 1, G2: 0) and no use of medication (G1: 2, G2: 1).

There was no difference in the need for complementation between groups on the third (G1: 0; G2: 11, $p = 0.5057$), fourth (G1: 5; G2: 9, $p = 0.6696$), fifth (G1: 10, G2: 7, $p = 0.5970$), sixth (G1: 3, G2: 7, $p = 0.1966$) or seventh (G1: 3, G2: 5, $p = 0.3576$) visit (Student t test). There was no difference in pain intensity (Table 2) or quality of life (Table 3). There was no difference in physical capacity on the first (G1: 0.7 ± 0.6, G2: 0.8 ± 0.6, $p = 0.4430$), second (G1: 1 ± 0.6, G2: 0, 9 ± 0, 5, $p = 0.8564$), third (G1: 1.1 ± 0.5, G2: 1.1 ± 0.5, $p = 1.000$), fourth (G: 1.2 ± 0, 4, G2: 1.1 ± 0.5, $p = 0.4203$), fifth (G1: 1.2 ± 0.6, G2: 1.1 ± 0.4, $p = 0.6234$), sixth (G1: 1.2 ± 0.6, G2: 1.20 ± 0.6, $p = 0.7197$)

Table 1 Demographic data (mean $\pm$ SD).

	G 1	G 2	p
Gender M:F	25:5	27:3	0.7065[a]
Age (years)	58.7 ± 12.4	57.5 ± 12.7	0.7071[b]
Weight (kg)	59.8 ± 13.8	58.6 ± 13.0	0.7301[b]
Height (cm)	166 ± 0.1	167 ± 0.1	0.7045[b]

G1, WHO ladder; G2, morphine in the 1st step.
[a] Fisher' test.
[b] Student t test.

Table 2 Pain intensity by visual analogue scale (cm; mean $\pm$ SD).

Follow-up	G 1	G 2	p
1st visit	5.8 ± 0.4[a]	5.8 ± 0.4[a]	0.5267
2nd week	4.6 ± 2.3[a]	4.6 ± 2.6[a]	0.9579
4th week	4.9 ± 2.1[a]	4.2 ± 2.3[a]	0.2019
6th week	3.7 ± 2.6[b]	3.7 ± 1.9[b]	0.9548
8th week	2.9 ± 2.6[c]	3.8 ± 2.5[c]	0.2307
10th week	2.5 ± 1.9[e]	3.4 ± 2.2[c]	0.1185
12th week	2.3 ± 2.1[f]	2.9 ± 2.5[d]	0.3400

G1, WHO ladder; G2, morphine in the 1st step.
Student t test.
[a] 30.
[b] 29.
[c] 28.
[d] 27.
[e] 24.
[f] 23.

Table 3 Quality of life.

Follow-up	G1	G2	p
1st visit	92.2 ± 11.7[a]	93.0 ± 10.5[a]	0.7816
4th week	88.3 ± 11.2[a]	89.7 ± 13.1[a]	0.6511
8th week	88.7 ± 13.2[b]	92.0 ± 10.4[b]	0.3003
12th week	91.1 ± 13.3[d]	91.0 ± 12.8[c]	0.9641

G1, WHO ladder; G2, morphine in the 1st step.
Student t test.
[a] 30.
[b] 28.
[c] 27.
[d] 23.

or seventh (G1: 1.2 ± 0.5, G2: 1.4 ± 0.7, p = 0443) visit (Mann–Whitney). Satisfaction with treatment was similar in both groups: on the second (G1: 20, G2: 24, p = 0.5275), third (G1: 22, G2: 27, p = 0.3288), fourth (G1: 22 G2: 28, p = 0.1056), fifth (G1: 26, G2: 26, p = 1), sixth (G1: 24, G2: 29, p = 1) and seventh (G1: 24, G2: 28, p = 1) visit (chi-square).

There was statistically significant difference between groups in the second visit to nausea (G1: 5, G2: 15, p = 0.0088), constipation (G1: 14, G2: 25, p = 0.0071), dizziness (G1, 6, G2: 14, p = 0.0376) and drowsiness (G1: 13, G2: 27, p = 0.0005) and there was also a statistically significant difference in the third visit to drowsiness (G1: 17, G2: 25; p = 0.05), always with greater frequency in G2 (chi-square).

Discussion

In this study, there was a reduction in pain intensity in the two groups, which suggests that the techniques are effective. In another study, patients receiving potent opioids had better pain control and greater satisfaction than the conventional group, but with more adverse effects.[11]

It is possible that the combination of paracetamol and morphine resulted in better analgesic effect. In other studies, the combination of potent opioids and non-opioids resulted in better control of pain.[12,14] However, in one study half the patients previously treated with the

combination of paracetamol with a potent opioid also obtained pain control without paracetamol; a substantial number of patients discontinued the use of this agent, because of the inconvenience of swallowing so many medications, and still maintained control of pain.[17,18] According to these data, G2 patients did not require very large doses of morphine for pain relief, even without paracetamol. For patients with moderate to severe pain who previously did not use opioids, a lower initial dose of morphine (15 mg/day) may be effective and well tolerated.[19]

There was no worsening of quality of life and physical capacity during the course of this study, but this did not reflect the negative impact of the disease. In another study, although patients receiving potent opioids have obtained better pain control, the quality of life and physical function gradually deteriorated.[14]

In this study there was no difference in patient satisfaction, which is an important form of assessment. Another important point is the incidence of adverse effects. In another study, patients receiving potent opioids were more satisfied, but had more adverse effects.[11] There was a lower incidence of nausea in patients with conventional treatment and in whom the doses of opioids were adjusted according to the severity of pain.[14] In this study, a higher incidence of adverse effects occurred when morphine was the first drug administered, which is in agreement with the validation of the WHO ladder.[3] However, no impairment of quality of life was observed in the second and third visits, which supports the use of morphine as a first drug. Effects such as nausea, vomiting and constipation can be managed with prophylactic antiemetics and laxatives. It is possible that the incidence of drowsiness and dizziness was comparable to that observed with the WHO ladder if the G2 patients had received lower doses of morphine and in association with paracetamol or dipyrone. The initial dose of morphine in G2 was fixed for all patients, which may have contributed to the higher incidence of adverse effects. The individualization of the initial dose based on the intensity of pain, with gradual increases, can reduce the incidence of adverse effects.

The motivation for this study was the small number of studies investigating an option to the WHO ladder for the

Table 4 Morphine dose (mg/day).

Visits	G1	G2	p
1st visit	–[a]	60.00 ± 0[a]	–
2nd week	–[a]	67.33 ± 32.48[a]	–
3rd week	71.54 ± 28.82[a]	80.00 ± 41.77[a]	0.5110
4th week	75.00 ± 29.56[b]	80.52 ± 50.15[b]	0.5986
5th week	80.00 ± 43.79[c]	87.86 ± 52.09[c]	0.5986
6th week	69.41 ± 43.08[e]	93.21 ± 59.69[c]	0.1598
7th week	79.38 ± 53.60[f]	98.15 ± 58.84[d]	0.3024

G1, with ladder; G2, without ladder.
Student t test.
[a] 30.
[b] 29.
[c] 28.
[d] 27.
[e] 24.
[f] 23.

treatment of cancer pain. About 30% of patients have moderate to severe pain and one reason may be the inappropriate prescription of opioids.[12]

The sample was obtained in two years and six months because of the difficulty of finding patients who attended to the inclusion criteria. In a similar study, the authors failed to include the number of the calculated sample.[11] In another study, patients with mild to moderate pain were included and would be excluded only if they were using potent opioids, and this facilitated the allocation.[14] It is believed that the sample size of this study is sufficient to reflect the effect of the medications according to WHO and of the use of morphine as a first medication. The patients' clinical conditions make it difficult to implement the protocol in this group with advanced cancer.

In this study, high incidence of head and neck tumors was diagnosed, unlike other studies,[11,14] but all patients attended to the inclusion criteria because the cancer was already in an advanced stage at diagnosis, with moderate pain, and never previously treated with opioids. In one study, two out of three patients with head or neck cancer had pain for six months before diagnosis.[20] The most commonly used painkiller before the first consultation was dipyrone, and in another study anti-inflammatory were the drugs most often used.[11]

It can be concluded that both methods of treating pain in advanced cancer patients are comparable, with the difference that patients receiving morphine as first medication have more adverse effects on the beginning of treatment. For selected patients with severe pain, the use of a potent opioid may be a more appropriate measure. The main limitation of this study is its impossibility of the use of a double-blind design. More studies are recommended to evaluate options for the analgesic ladder (Table 4).

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Kanavos P. The rising burden of cancer in the developing world. Ann Oncol. 2006;17:15–23.
2. Paice JA. Chronic treatment-related pain in cancer survivors. Pain. 2011;152:S84–9.
3. Ventafridda V, Tamburini M, Caraceni A, et al. A validation study of the WHO method for cancer pain relief. Cancer. 1987;59:850–6.
4. Apolone G, Corli O, Caraceni A, et al. Pattern and quality of care of cancer pain management. Results from the Cancer Pain Outcome Research Study Group. Br J Cancer. 2009;100:1566–74.
5. Colson J, Koyyalagunta D, Falco FJE, et al. A systematic review of observational studies on the effectiveness of opioid therapy for cancer pain. Pain Phys. 2011;14:E85–102.
6. Reid CM, Gooberman-Hill R, Hanks GW. Opioid analgesics for cancer pain: symptom control for the living or comfort for the dying? A qualitative study to investigate the factors influencing the decision to accept morphine for pain caused by cancer. Ann Oncol. 2008;19:44–8.
7. Fairchild A. Under-treatment of cancer pain. Curr Opin Support Palliat Care. 2010;4:11–5.
8. Breivik H, Cherny N, Collett B, et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. Ann Oncol. 2009;20:1420–33.
9. Costantini M, Ripamonti C, Beccaro M, et al. Prevalence, distress, management, and relief of pain during the last 3 months of cancer patients' life. Results of an Italian mortality follow-back survey. Ann Oncol. 2009;20:729–35.
10. Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. A review of published literature. Ann Oncol. 2008;19:1985–91.
11. Maltoni M, Scarpi E, Modonesi C, et al. A validation study of the WHO analgesic ladder: a two-step vs three-step strategy. Support Care Cancer. 2005;13:888–94.
12. Klepstad P, Kaasa S, Cherny N, et al. Pain and pain treatments in European palliative care units. A cross sectional survey from the European Association for Palliative Care Research Network. Palliat Med. 2005;19:477–84.
13. Ferreira KASL, Kimura M, Teixeira MJ. The WHO analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it? Support Care Cancer. 2006;14:1086–93.
14. Marinangeli F, Ciccozzi A, Leonardis M, et al. Use of strong opioids in advanced cancer pain: a randomized trial. J Pain Symptom Manage. 2004;27:409–16.
15. Fleck MPA, Louzada S, Xavier M, et al. Aplicação da versão em português do instrumento abreviado de avaliação da qualidade de vida ''WHOQOL-brief''. Rev Saúde Pública. 2000;34:178–83.
16. Myers J, Gardiner K, Harris K, et al. Evaluating correlation and interrater reliability for four performance scales in the Palliative Care Setting. J Pain Symptom Manage. 2010;39:250–8.
17. Dios PD, Lestón JS. Oral cancer pain. Oral Oncol. 2010;46:448–51.
18. Axelsson B, Stellborn P, Ström G. Analgesic effect of paracetamol on cancer related pain in concurrent strong opioid therapy. A prospective clinical study. Acta Oncol. 2008;47:891–5.
19. Israel FJ, Parker G, Charles M, et al. Lack of benefit from paracetamol (acetaminophen) for palliative cancer patients requiring high-dose strong opioids: a randomized, double-blind, placebo-controlled, crossover trial. J Pain Symptom Manage. 2010;39:548–54.
20. Mercadante S, Porzio G, Ferrera P, et al. Low morphine doses in opioid-naive cancer patients with pain. J Pain Symptom Manage. 2006;31:242–7.