

Evaluation of intestinal habits of cancer patients under morphine for pain control*

Avaliação do hábito intestinal em pacientes com câncer que utilizam morfina para o controle da dor

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SUMMARY

BACKGROUND AND OBJECTIVES: There are few data in the literature on intestinal constipation secondary to morphine in cancer patients. This study aimed at evaluating intestinal habits of cancer patients under morphine.

METHOD: This is a prospective non-randomized study carried out from February to November 2007. All patients had cancer, over 4 years of age and were under morphine for pain control. Patients received laxatives 24 hours after starting with morphine. Intestinal habits were evaluated through a structured questionnaire. When needed, feces were rectally or orally desimpacted.

RESULTS: Twenty-two cancer patients aged between 5 and 35 years (mean 16.7 years) were admitted, of whom 63.6% were under palliative care. During the first week under morphine and lactulose, 40.9% of patients were constipated. In the second and third weeks, constipation was present in 38.8% and 16.6% of patients, respectively. Treatment was able to control constipation in 50% of cases.

CONCLUSION: Constipation was frequent however the specific attention to their intestinal habits has increased adherence to laxatives and has decreased the formation of fecal impaction.

Keywords: Intestinal constipation, Pain, Morphine, Neoplasia.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Há poucos dados na literatura sobre constipação intestinal secundária ao uso de morfina em pacientes com câncer. O objetivo deste estudo foi avaliar o hábito intestinal de pacientes com câncer em uso de morfina.

MÉTODO: Estudo prospectivo, não aleatório, realizado no período de fevereiro a novembro de 2007. Todos os pacientes tinham câncer, idade superior a quatro anos e utilizavam morfina para o controle de dor. Após 24h do início da morfina os pacientes receberam laxantes. A avaliação do hábito intestinal foi realizada através de um questionário estruturado. Quando necessário, foi realizado desimpactação das fezes por via retal ou oral.

RESULTADOS: Foram admitidos 22 pacientes com câncer e idade entre cinco e 35 anos (média 16,7 anos), dos quais 63,6% estavam em cuidados paliativos. Na primeira semana do uso de morfina e lactulona, 40,9% dos pacientes ficaram constipados. Na segunda e terceira semanas, a constipação ocorreu em 38,8% e 16,6%, respectivamente. Com o tratamento adotado foi possível controlar o quadro de constipação em 50% dos casos.

CONCLUSÃO: A constipação intestinal foi frequente; entretanto, a atenção específica ao hábito intestinal destes pacientes aumentou a adesão aos laxantes e reduziu a formação do fecaloma.

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INTRODUCTION

Pain is common in cancer patients and is considered the most prevalent and disabling symptom in this population, especially in case of metastases or relapses^{1,2}. The World Health Organization (WHO) indicates morphine to treat moderate to severe pain of cancer patients³. However, although effective, the treatment with morphine is often associated to side effects, such as constipation^{4,5}. There are few data in the literature about constipation secondary to morphine among pediatric cancer patients. This symptom is more commonly studied in adults⁶. However, after studying adverse morphine effects in 122 Brazilian cancer children⁷, authors have observed that 72.9% of cases had constipation. Although being a relatively common manifestation in patients under opioids, it is worsened by several other factors such as malnutrition, dehydration and simultaneous use of other drugs, which are especially present in metastatic oncologic patients under palliative care⁸.

Constipation is a challenge for the oncologic practice because it is often neglected by health professionals and caregivers, although being associated to several other symptoms, such as discomfort, abdominal pain, nausea, vomiting, fecal impaction with or without anal injury^{4,5}, which invariably impact global health and quality of life of cancer patients, in addition to increasing the use of other drugs for relief or symptomatic treatment of symptoms and the rate of complications and costs related to such interventions.

Considering the relevance of the subject and that experience in the treatment of opioid-induced constipation in children is scarce, this study aimed at evaluating intestinal habits of cancer patients under morphine.

METHOD

Prospective, cohort, non randomized, single-armed study carried out from February to November 2007 with cancer patients followed by the pain outpatient clinic, Pediatric Oncology Institute (IOP), Federal University of São Paulo-SP. Participated in this study cancer patients under morphine for at least one week, indicated to control baseline cancer-related pain, with at least four years of age. Patients with clinical instability were excluded. The Free and Informed Consent Term was obtained from all patients/ guardians.

The intestinal habit of patients included in the study was

evaluated before admission to the study, 72 hours after admission and then in weeks 1, 2 and 3, depending on the time they remained under the analgesic.

According to literature criteria, constipation was considered when: hard stools elimination, in the shape of cymbals, pebbles, cylindrical or with cracks; difficulty or pain to evacuate; or decreased number of evacuations per week (< 3 times) or elimination of bulky stools which clog the toilet; or evidences of fecal impaction.

Indications for morphine use and withdrawal, initial doses and dose adjustments were established according to the pain treatment protocol used for IOP's routine. Initial morphine dose was oral 0.3 mg/kg every 4 hours.

Patients started treatment with osmotic laxative 24 hours after starting with morphine: syrup lactulose solution in the presentation of 667 mg/mL, in the dose of 1 mL/kg/day until the maximum of 60 mL/day.

Fecalomas were systematically investigated through physical evaluation or, when needed, with plain abdominal X-rays. Treatment of fecaloma by fecal desimpaction was oral with 3350 polyethylene glycol (PEG 3350 Muvinalax®), 1.5 g/kg/day for three days (maximum dose of 100 g/day), or rectal using 10% glycerin solution (10 mL/day). Rectal desimpaction was indicated when oral route was unfeasible due to suspended diet or intolerance to oral PEG 3350. To be submitted to rectal desimpaction, patients had to have platelet counts above 50,000 / μ L and more than 500 granulocytes / μ L.

Laxative intervention outcomes were: 1) evacuation at least every two days, with no pain or difficulty to evacuate and 2) lack of fecal impaction during morphine use. Efficacy analyses were carried out weekly, according to the time patients remained in the study. Patients with unsatisfactory therapeutic response received therapeutic options, such as the association of other laxatives or replacement of morphine by different opioids.

This study was approved by the Ethics Committee, Federal University of São Paulo (UNIFESP) under number 1502/2006.

RESULTS

Participated in this study 22 patients under morphine and meeting eligibility criteria. Mean age of patients was 16.7 years (5 to 35 years), being 54% males. From evaluated patients, 63.6% (14/22) had no possibility of being cured and were receiving palliative chemotherapy (Table 1).

At admission, 27.2% of patients had constipation, being recommended the use of lactulose (1 mL/kg/day) for all cases. Two patients needed bisacodyl due to intolerance to lactose. After 72 hours, all patients

Table 1 – Clinical characteristics of patients (n = 22)

Patient	Gender	Age (years)	Diagnosis	Impossible to be Cured
1.	M	23	Soft tissue sarcoma	Yes
2.	M	8	Neuroblastoma	Yes
3.	M	16	CNS Tumor	No
4.	F	9	Osteosarcoma	Yes
5.	M	35	Osteosarcoma	Yes
6.	F	15	Ewing Tumor	No
7.	F	7	Soft tissue sarcoma	Yes
8.	F	13	Soft tissue sarcoma	No
9.	F	10	Soft tissue sarcoma	No
10.	M	16	Osteosarcoma	Yes
11.	M	5	Non-Hodgkin lymphoma	No
12.	M	13	Wilms Tumor	No
13.	M	17	CNS Tumor	Yes
14.	F	14	Osteosarcoma	No
15.	F	18	Ewing Tumor	Yes
16.	M	31	Osteosarcoma	Yes
17.	F	14	Neuroblastoma	Yes
18.	M	11	Neuroblastoma	Yes
19.	F	10	Soft tissue sarcoma	No
20.	M	16	Osteosarcoma	Yes
21.	M	5	Non-Hodgkin lymphoma	No
22.	M	13	Wilms Tumor	No

CNS = central nervous system; M = male; F = female

were under laxatives; however, two out of 22 cases had fecaloma needing rectal desimpaction with glycerin solution and maintenance with bisacodyl (10 mg/day), which stimulates bowel movements.

During the first week, 40.9% of patients had constipation being two with fecalomas. Four out of these nine patients did not adhere to prescription and had lower lactulose doses. For patients with poor adhesion to treatment, lactulose dose was maintained and medical recommendations were reinforced. For the other four patients evolving with constipation, lactulose dose was increased to 2 mL/kg/day.

In the second week, four out of 22 patients left the study because morphine was withdrawn. Seven out of 18 remaining patients (38.8%) had constipation and four of them presented fecaloma, which was desimpacted with oral PEG 3350 in two cases and with rectal glycerin solution in two patients. One of these two patients died due to progression of baseline disease.

In the third week, morphine was withdrawn for six patients. From the 12 patients remaining in follow up, 83% remained without constipation and 16.6% of them had constipation signs.

One refractory patient was identified as not adhering to the lactulose treatment and maintenance with PEG 3350 (0.5 g/kg/Day) was started with good acceptance and favorable response in future evaluations. The other patient had fecal impaction resolved with rectal glycerin solution. Constipation in this case was considered refractory to normal treatment being necessary to replace the opioid. Patient's intestinal habit was normalized with intradermal fentanyl. One patient died in the third week due to baseline disease progression.

During the study period, nine fecaloma episodes were diagnosed. Four patients using oral PEG 3350 for fecal desimpaction had favorable response before the third day of medication and no side effects were observed. With regard to oral lactulose used for maintenance, two

patients had nausea and the drug was replaced. Table 2 shows intestinal habits and presence of fecalomas.

recommended laxatives when starting with morphine, we have observed that only 36.4% of patients adhered

Table 2 – Frequency of intestinal constipation and presence of fecalomas (n = 22).

	72 hours	First Week	Second Week	Third Week
Intestinal Constipation	6/22(27%)	9/22(41%)	7/18(38.8%)	2/12 (16%)
Presence of fecaloma	2/22 (9%)	2/22(9%)	4/18 (22.2%)	1/12 (8.3%)
Fecal desimpaction	2 rectal	2 oral	2 rectal 2 oral	1 rectal

DISCUSSION

Constipation diagnosis and treatment of cancer patients have major peculiarities. In these cases, several factors may change intestinal habits, such as poor food acceptance, dehydration, walking difficulties, use of numerous drugs, and clinical and emotional instability. Among drugs, opioids play a relevant role on constipation⁸⁻¹⁰. These aspects make cancer patients a group with differentiated attention needs and any sign or symptom of constipation should be considered^{11,12}. The complex clinical situation of cancer patients impairs the collection of information to diagnose the cause of intestinal habit changes as well as to determine the effective treatment.

Our study group was heterogeneous with different types of cancer, different evolution times, simultaneous drugs, dose and duration of morphine treatment. Most patients (63.6%) had no possibility of being cured and presented a large number of interurrences during the evaluation of intestinal habits, such as infections, tumor progression, and loss of anal sphincter control. It has to be stressed that the clinical status of cancer patients is dynamic, both with regard to baseline disease and to existing comorbidities⁷. Constipation secondary to morphine is not exception to this rule and our study has observed the need for regular and frequent intestinal habit follow up. The incidence of constipation is high (40% to 60%) after starting with opioids, regardless of the type of morphine prescribed, be it immediate or slow release¹². However, in spite of the frequency and the difficulty of treating it, constipation secondary to morphine is poorly valued by health professionals^{13,14}. No studies were found in the Brazilian literature systematically evaluating the presence of constipation and the effectiveness of its treatment in children under opioids. Studies with adult patients are useful¹⁵, however they cannot simply be extrapolated as paradigm for children and adolescents with their own physical, physiological and psychological characteristics. Although the pain control protocol used in this study

to prescription. In practice, there has been poor adherence to laxatives probably due to dysgeusia caused by cancer treatment and the need for several simultaneous drugs. After the beginning of this study, the adherence to recommended laxatives was very satisfactory and in the second and third study weeks only one case of non-adherence was detected. This result reinforces the need for health professionals careful attention to diagnose, follow up and treat morphine-induced constipation.

Drugs used in this study (laxatives and fecal desimpaction) have followed the recommendations for the treatment of children with chronic severe functional constipation according to approaches normally adopted in Brazil, which are in line with the North-American therapeutic guidelines¹⁶.

Studies have found that constipation is present between the 4th and the 8th day under morphine¹². However, in our study, probably due to the small sample size, there has been no relationship between constipation and the time morphine was been used. Constipation secondary to morphine was observed in 40.9% of patients in the first week, in 38.8% in the second week and in 16.6% in the third week.

In spite of the small number of patients, these results may be considered similar to the international literature^{17,18} and are attributed, in addition to the drugs, to the fact that the study was prospective and that specific attention was given to constipation.

It is worth reminding that, according to the literature, constipation secondary to morphine affects 70% to 80% of terminal patients and is difficult to contro^{17,13,14,19}. Our study has shown that it was possible to control constipation for most patients. However, the effectiveness of the therapy should be analyzed with caution considering that, for ethical reasons, it would be impossible to have a control group. In addition, 40% of patients had constipation in spite of preventive measures, suggesting the need for studies with laxatives acting on

specific intestinal receptors with higher effectiveness and few side effects²⁰⁻²².

During the study, nine clinical fecaloma were diagnosed and fecal desimpaction was a difficult stage of patients' management, generating pain and discomfort. The elimination of impacted stools was achieved with rectal drugs or high dose oral laxatives. The acceptance and the efficacy of this procedure are critical for the evolution of the maintenance treatment with oral laxatives.

Rectal desimpaction should not be done under certain clinical conditions, such as leucopenia, low platelet count, anal injury, severe immunodepression and without patients' previous consent. In these cases, the option is high-dose oral laxative which, in our study, was successfully used for three times. The effectiveness of oral desimpaction with PEG 3350 has been described in the literature²³. In 2006, the American Society for Pediatric Gastroenterology, Hepatology and Nutrition has recommended the use of oral laxatives in high doses for fecal desimpaction, however stressing the need for further studies in the pediatric age group.

In one patient, constipation was refractory to treatment and morphine had to be replaced by intradermal fentanyl in the third week. The replacement of one opioid by another should be considered to control refractory or unbearable side effects²⁴. The choice of the drug to replace morphine varies according to the experience and the availability of different medical centers. μ receptor agonist opioids have the same action mechanism; however, they are different in pharmacodynamics and in the affinity for the receptor, which could explain differences in analgesia and side effects²⁵.

Nevertheless, the regular use of osmotic and stimulating laxatives in adequate doses has improved constipation-related symptoms in 50% of patients, which is in line with the literature^{26,27}. In three weeks of follow up it was possible to evaluate the intestinal habit profile of patients under morphine, confirming the high incidence of constipation, its difficult control and the need for an organized multidisciplinary protocol to diagnose, prevent and treat constipation secondary to morphine.

Early preventive treatment with laxatives, guidance and regular follow up may decrease the incidence of severe constipation with fecal impaction. Further controlled studies with a higher number of cases are needed to develop effective multiprofessional therapeutic practices to decrease the distress of cancer patients under morphine.

CONCLUSION

Constipation was frequent in patients under morphine,

however, the protocol with specific attention to constipation has increased patients' adhesion to laxatives and, as a consequence, has decreased the incidence of fecalomas.

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