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CONSTIPATION IN PATIENTS TREATED WITH OPIOIDS: AN INTEGRATIVE REVIEW

Constipação intestinal em pacientes tratados com opioides: uma revisão integrativa

Estreñimiento en pacientes asistidos con opioides: una revisión integrativa

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ABSTRACT

Objective: To investigate the impact of Opioid-Induced Constipation (OIC) in the literature through the identification of the risk factors, symptoms and treatments. **Methods:** We carried out a review of scientific publications available in the Virtual Health Library (VHL), the Scientific Electronic Library Online (SciELO), the Latin-American and Caribbean Center on Health Sciences Information (LILACS) and the Medical Literature Analysis and Retrieval System Online (MEDLINE) databases. The search was carried out using the descriptors "analgesic opioids", "constipation" and "pain" in English, Portuguese and Spanish, correlated or isolated. We searched for publications dating from 2011 to 2016 that investigated patients receiving treatment for pain with continuous use of opioids and with constipation as a clinical outcome. **Results:** The results highlighted constipation as the main secondary effect of opioids, which are very important for the control of cancer pain, and identified the risk factors for the disease. In addition, patients who were well served by health professionals presented better adherence to OIC treatment. **Conclusion:** The OIC control provides abdominal comfort, self-care and reduction in treatment costs. The importance of training health professionals and promoting prevention and periodic monitoring of patients should be highlighted. In addition, diet therapy and drug therapy should be provided early.

Descriptors: Analgesics, Opioid; Constipation; Pain; Neoplasms.

RESUMO

Objetivo: *Investigar na literatura o impacto da constipação intestinal induzida por opioides (CIO) por meio da identificação dos seus fatores de risco, sintomas e tratamentos.* ***Métodos:*** *Realizou-se, entre fevereiro e março de 2016, um levantamento de publicações científicas nas bases de dados eletrônicas Biblioteca Virtual em Saúde (BVS), Scientific Electronic Library Online (SciELO), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) e Medical Literature Analysis and Retrieval System Online (MEDLINE), pesquisadas por meio dos descritores "analgésicos opioides", "constipação intestinal" e "dor", apresentados nos idiomas inglês, português e espanhol, correlacionados ou isolados, no período de 2011 a 2016, que investigassem pacientes em tratamento da dor com uso contínuo de medicamentos opioides e com desfecho clínico de constipação intestinal.* ***Resultados:*** *Os estudos apontaram a constipação intestinal como principal efeito secundário ao uso de opioides, os quais são muito importantes para o controle da dor de origem oncológica, assim como identificaram os fatores de risco para o surgimento da doença. Além disso, pacientes que foram bem assistidos por profissionais de saúde apresentaram melhor adesão ao tratamento da CIO.* ***Conclusão:*** *O controle da CIO proporciona conforto abdominal, autocuidado e redução nos custos do tratamento, ressaltando que deve haver capacitação dos profissionais de saúde, prevenção e acompanhamento periódico, além da precocidade dos tratamentos dietoterápico e medicamentoso.*

Descritores: *Analgésicos Opioides; Constipação Intestinal; Dor; Neoplasias.*

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RESUMEN

Objetivo: *Investigar en la literatura el impacto del estreñimiento inducido por opioides (EIO) a través de la identificación de sus factores de riesgo, síntomas y tratamientos.* ***Métodos:*** *Se realizó entre febrero y marzo de 2016 una búsqueda de publicaciones científicas en las bases de datos electrónicas Biblioteca Virtual en Salud (BVS), Scientific Electronic Library Online (SciELO), Literatura Latino-Americana y del Caribe en Ciencias de la Salud (LILACS) y Medical Literature Analysis and Retrieval System Online (MEDLINE) investigadas a través de los descriptores "analgésicos opioides", "estreñimiento" y "dolor" en los idiomas inglés, portugués y español de manera individual o asociadas en el período entre 2011 y 2016 sobre investigaciones con pacientes en tratamiento del dolor en uso continuo de medicamentos opioides y desenlace clínico de estreñimiento.* ***Resultados:*** *Los estudios señalan el estreñimiento como principal efecto secundario del uso de opioides los cuales son muy importantes para el control del dolor de origen oncológico así como identificaron los factores de riesgo para el aparecimiento de la enfermedad. Además de eso, los pacientes que fueron bien asistidos por profesionales sanitarios presentaron más adhesión para el tratamiento del EIO.* ***Conclusión:*** *El control del EIO promueve el conforto del abdomen, el autocuidado y la reducción de los costes de tratamiento resaltando la necesidad de capacitación de los profesionales sanitarios, la prevención y el seguimiento periódico, además de la precocidad de los tratamientos de dieta y de medicamentos.*

Descriptores: *Analgésicos Opioides; Estreñimiento; Dolor; Neoplasias.*

INTRODUCTION

Opioids are understood as any natural, semisynthetic or synthetic compound with properties similar to those of the endogenous opioids and that specifically bind to opioid receptors (*mu, kappa, delta* and *epsilon*), which are important in the normal regulation of pain sensation[1].

Opium is an original substance in the pharmacological group of opiates, extracted from the poppy (*Papaver somniferum*). Historically, it has been reported that the use of opioids goes back more than 4,000 years[2]. In many historical events, the use of opium is mentioned, as in the opium war, in China, where its use was spread through smoking, and in the American civil war, with the massive use of opium orally, and morphine, subcutaneously, in soldiers wounded in combat, or as a way of supporting the conditions of battle[3].

Currently, opioids are used in situations of pain control in patients with neuropathic or mixed pain, low back pain, headache, neuralgia, arthritis, insomnia, inappetence, pre- and postoperative conditions, anesthesia, major burns, polytrauma[4] and oncology patients with or without therapeutic possibility[5].

Pain relief in cancer patients requires the use of this class of drugs to promote an improvement in the quality of life of these individuals. However, the administration of these drugs produces side effects[6], among which we can highlight the gastrointestinal tract infection, which can lead to constipation[7].

In a study of patients who received opioids for palliative pain treatment, it was observed that constipation occurred in more than half of the patients, being almost always persistent, even with the use of laxatives[8]. Conversely, by means of a common observation, in an outpatient pain clinic of a reference hospital for cancer treatment in the North/Northeast regions, during interventions of doctors and multiprofessional residency students to opioid patients, an association was observed between adherence to treatments and bowel rehabilitation. Thus, this observation brought the need to understand the actual dimension of the opioid-constipation relationship. Therefore, the present study aimed to investigate the impact of Opioid-Induced Constipation (OIC) in the literature through the identification of the risk factors, symptoms and treatments.

METHODS

The proposed study is an integrative review of literature, which is a method for analyzing it broadly, promoting a solid theoretical foundation, which can contribute to discussions about methods and research results, and pointing out knowledge gaps that need to be fulfilled through new studies[9].

Thus, a survey of scientific publications was conducted between February and March 2016, in the electronic databases Virtual Health Library (VHL), Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature in Health Sciences (LILACS) and Medical Literature Analysis and Retrieval System Online (MEDLINE), using the descriptors " analgesic opioid ", "constipation" and "pain", in English, Portuguese and Spanish, correlated or isolated, in the period from 2011 to 2016, which investigated patients in pain treatment with continuous use of opioid drugs and with constipation as a clinical outcome. The guiding question of the research was: how strong is the impact of drug interaction of opioids on constipation?

As exclusion criteria, studies on animal, without the use of opioids or without clinical outcome of constipation, as well as bibliographic reviews, theses, dissertations, monographs and texts that were duplicated in more than one database were rejected.

Screening began after the identification of the articles that included the selected descriptors and met the inclusion criteria. Next, a selective reading of the articles was carried out, starting from the reading of the titles and abstracts, followed by the exploratory, analytical and interpretative analysis of the articles in full, with the purpose of making some considerations about the object of study of this research.

RESULTS

Initially, 48 articles were found, but only 10 included the eligibility criteria. The scientific articles were respectively organized and described in table I according to author/year, objective and main results.

Among the scientific articles selected, six were presented in English, two in Portuguese and two in the Spanish language. With regard to the objectives of the articles, 70% discuss issues related to the symptoms of constipation, but also address other issues, such as risk factors, drug and diet therapy, financial costs and the different perceptions of treatment.

Chart I - Articles description in accordance with author, year, objective, study population and results.

Author/Year	Objective	Study population	Results
Dzierżanowski; Ciałkowska-Rysz, 2015[10]	To evaluate the correlation between FqBM and risk factors for constipation in palliative care patients.	Patients in palliative care at three specialized centers submitted to questionnaires on the symptoms of intestinal dysfunction, behavioral risk factors and opioid use.	The main risk factors for constipation in palliative care patients were: insufficient fluid and food intake, inadequate privacy conditions, dependence on a caregiver, and overall poor performance as well.
Chumpitaz-Corredor; Lara-Solares, 2012[11]	To report the effect of subcutaneous (SC) administration of MTNX (12 mg) for relief from opioid-induced constipation.	Terminal patients of the SZNIMSN, who were evaluated during admission by the pain and palliative care clinical team and presented constipation secondary to the treatment with opioids.	All patients had defecation after MTNX administration. There was no correlation between the opioid dose and the MTNX response time. There was no correlation between the dose of opioid and the days of constipation, nor between days of constipation and response to MTNX.
Gálvez et al., 2014[12]	To analyze the prevalence and severity of OIBD symptoms.	Outpatients diagnosed with cancer pain or chronic non-oncologic pain treated with a single opioid.	Patients treated with opioid had a high frequency of bowel disorders. Constipation was the most common symptom, highlighting the need for new treatment strategies.
Takemoto et al, 2011[13]	To estimate the prevalence of constipation concomitant with opioid treatment and to compare the use of resources and costs in patients treated with opioids, with and without constipation, from the perspective of the private payer in Brazil.	Patients with constipation or undergoing related procedures during opioid treatment were identified by an algorithm in a longitudinal database of health insurance companies, divided into four groups: G1 not treated with opioids without constipation; G2- not treated with opioids with constipation; G3- treated with opioids without constipation; G4- treated with opioids with constipation.	Patients with constipation who underwent opioid treatment imposed a greater economic burden than patients without this condition.

Laugsand et al., 2011[14]	To examine the adequacy of treatment for constipation, nausea, depression and lack of sleep, and factors associated with inadequate symptom control in cancer patients undergoing opioid treatment.	Patients who received strong opioids for cancer pain, recruited from 17 centers in 11 European countries.	Most cancer patients had inadequate, ineffective, or absent treatment. There were subgroups of patients at particular risk (constipation, nausea, depression and poor sleep) for inadequate treatment, who may need special attention from HCPs for proper symptom control.
Tai et al., 2016[15]	To evaluate the severity of symptoms of advanced cancer patients in a palliative care unit and explore the factors associated with symptom improvement.	Patients of a palliative care unit in Taiwan.	The severity of symptoms decreased during the first week in the palliative care unit. Additionally, sex differences and primary cancer sites may contribute to different degrees of symptom improvement.
Nunes; Garcia; Sakata, 2014[16]	To evaluate the use of morphine as the first drug for treatment of moderate oncologic pain in patients with advanced disease and/or metastasis, as an option to the recommendations of the analgesic ladder advocated by WHO.	Patients with cancer, aged ≥ 18 years and without use of opioids. Division into two groups: G1- treated with drugs according to the analgesic ladder; G2 - treated with morphine.	The use of morphine as the first drug for treatment of pain did not promote better analgesic effect than the analgesic ladder recommended by the WHO and there was a higher incidence of adverse effects.
Marmo et al., 2012[17]	To evaluate bowel habit of cancer patients using morphine.	Oncology patients monitored at the IPO pain outpatient clinic of the Federal University of São Paulo, SP.	Constipation was frequent, however, specific attention to bowel habits of these patients increased adherence to laxatives and reduced the formation of fecaloma.
Feudtner et al., 2014[18]	Compare patients who received Senna with similar patients who received other intestinal/oral medicine and determine the subsequent risk of "problematic constipation.".	Cancer patients ≤ 20 years of age who, during hospitalization, were exposed to seven or more days of consecutive opioid use and exposed to at least one intestinal/oral medicine during the first or second day of the reference period.	Initiating therapy with Senna, in comparison to other intestinal/ oral medicines, diminishes the subsequent risk of markers of problematic constipation in this population.
Locasale et al., 2016[19]	Describe the understanding of HCP by means of OIC patients' report of experiences. To assess the degree of perception agreement or disagreement between the patients and their health professionals who treat OIC and the impact on clinical outcomes.	Patients aged 18-85 years who received daily treatment with opioids for ≥ 4 weeks to treat chronic non-oncologic pain in the presence of OIC.	The importance and severity of OIC are perceived differently by patients and their HCP, disagreement that complicates the management of pain and demonstrates the need for greater communication.

OIC = Opioid-induced constipation; OIBD = Opioid-induced bowel dysfunction; FqBM = Frequency of Bowel Movements; SZNIMSN = Salvador Zubirán National Institute of Medical Sciences and Nutrition; MTNX = Methylnaltrexone; IPO= Institute of Pediatric Oncology; WHO = World Health Organization; HCP = Health Care Providers.

DISCUSSION

The results found in this study pointed constipation as the main secondary effect to the use of opioids during pain treatment in all articles analyzed[10-19]. In seven studies the reason for opioid use was directly related to the control of pain with exclusively

oncologic cause[10,11, 14-18], in two others the reason was mixed, oncologic/non-oncologic[12,13], and only one was exclusively non-oncological[19]. Additionally, the majority of the studied population had a mean age greater than or equal to 60 years[10,11,14,15], information that seems to suggest a positive correlation between cancer/old age for the use of opioids/OIC.

OIC is one of the causes of unresolved pain in patients during pain management. Normally, its responsiveness to regular laxatives is poor and this may be an obstacle to effective pain management[10]. Furthermore, unlike other side effects, it does not develop tolerance over time, and increases with duration of treatment[10-12], being the most difficult problem during pain management with use of opioids[10].

One article pointed out that patients reported some degree of negative impact due to gastrointestinal effects after using opiods in aspects such as work, sleep quality, social relations, daily activities, quality of life and general mood, and also highlighted constipation as the more frequent cause for abandonment of long-term treatment[12].

From a financial cost perspective, it was observed in a study that OIC patients reported significantly more visits to the doctor and alternative care, besides being more likely to be in palliative care, which favors the increase in treatment costs, reinforcing the fact that, comparatively, OIC poses a greater influence on the use of resources and higher costs than patients without this condition[13].

To better understand the problem of this condition, the discussion of this research was divided into five thematic axes: symptoms and risk factors, cancer patients, drug therapy, diet therapy and impact of health professionals on treatment.

Symptoms and risk factors

Three articles define OIC as a symptom of opioid-induced bowel dysfunction (OIBD), which is a common complication of opioid treatment in chronic pain, characterized by reduced gastric emptying, stomach cramps, edema, reduced bowel movements and excessively hardened faeces[10-12]. Among the symptoms, constipation is the most common and debilitating OIBD, with most prevalence estimates based only on the frequency of this primary symptom[12].

Six studies report that, in addition to constipation, other adverse effects, secondary to pain therapy, commonly occur and include: drowsiness, nausea, vomiting, acidity, flatulence, anorexia, distension and abdominal pain[10-12,14-16], which, sometimes, limit the benefit of the medicine and may lead to abandonment of treatment[12].

When administered for pain analgesia, opioid drugs have affinity for *mu*, *delta* and *kappa* receptors, which are responsible for the peripheral and central action of these drugs. However, they present selectivity problems, causing adverse effects to the expected, being *mu* receptor responsible for OIC[12]. It has central action in the intestine and, when stimulated by the drug, influences the inhibition of intestinal peristalsis, decreasing motility[11].

Two papers suggest that OIC diagnosis should be based on objective and subjective symptoms. Objective symptoms, identified by less than three bowel movements per week, and subjective symptoms, identified by effort of difficult elimination, excessively hard stools, with reduced volume, sensation of incomplete evacuation, abdominal discomfort, gastric fullness and measures to facilitate the excretion of the fecal matter[10,12].

There are risk factors for the onset of OIC that make it difficult to diagnose[14]. Four articles attributed these factors to debilitating aspects in patients' functional capacity, such as: immobilization (especially in dorsal decubitus), low physical activity, advanced age, insufficient acceptance of fluids and food, abdominal cancer, lack of privacy, and clinical and emotional instability[10,11,14,17]. One study defined that the factors are subject to the presence of other gastrointestinal symptoms, and these, in turn, depended on the duration of pain, suggesting that the incidence of OIC probably occurs in patients in chronic pain treatment for 12 months or longer[12].

When the reduction in functional capacity occurs, patients spend more time bedridden. Subsequently, appetite and thirst get reduced, so that, as the disease progresses, they become dependent on their caregivers. When the condition intensifies, they become more susceptible to uncomfortable situations for defecation. Thus, it is already possible to anticipate the diagnosis of constipation from the deterioration of a patient's condition, which is important for creation of prophylactic actions. It is also worth noting that, regardless of the care regime, whether hospital or home, and the immobility, whether complete or partial, (wheelchair users or those who do not perform all movements), patients are affected to a similar degree by these risk factors[10].

Defecation is a basic right to the dignity and honor of patients, an intimate act that must be respected. When privacy is not guaranteed, patients may be restrained in relation to bowel movements, leading to constipation by postponing defecation. This condition usually occurs among hospital patients, especially those in palliative care, since they are the most impaired, as the evacuation is liable to occur under the assistance of the healthcare team. In many cases, it is possible to reshape care and create a supportive environment in order to ensure the privacy of these patients[10].

Cancer patients

Considering that most of the population studied in the articles were elderly and have some type of cancer[10,11,14,15], it is possible to infer that age may present as a risk factor, for both constipation and cancer. The disease, when installed, can promote cancer pain and the search for pain control through the use of opioids, which, as a consequence, can cause constipation.

Despite the recognition of old age as a risk factor for OIC, this does not mean that children and adolescents with cancer, treated with opioids, are immune to this condition; therefore, treatment recommendations should not be extrapolated to this population, which requires differential treatment to control the disease, since it presents its own physical, physiological and psychological characteristics[17].

Patients with cancer have a dynamic clinical situation, in relation to both the underlying disease and existing comorbidities, being subject to the same risk factors for OIC already mentioned, hindering the diagnosis of the possible causes of intestinal transit alteration and consequent effective treatment[17]. However, symptom control is encouraged and should be treated as early as possible, because of the functional status deterioration when constipation is established[11], besides allowing the understanding of the problem and improvement of the clinical management[12].

A study that separately analyzed cancer patients with and without constipation found that, comparatively, patients with cancer and constipation generated higher costs of treatment than patients with cancer and no constipation[13].

In advanced cancer, clinical conditions can become markedly deteriorated in the terminal phase, resulting in sudden worsening of symptoms, so the rapid and effective management of these symptoms is essential to ensure adequate comfort and a high "quality of death"[15].

Drug therapy

Two studies stated that OIC adverse effects would be controlled with the prophylactic use of laxatives, and that laxative prescribing is recommended early in treatment[16,17]. Another study indicates that senna-based laxatives are well tolerated in children and adults on prolonged course of opioid therapy, provided that there are no contraindications, having little side effect and low financial cost compared to other pharmacological agents and techniques used to prevent or treat constipation, such as enemas or exposures to abdominal imaging[18].

Three studies consider it important that recommendations for the symptomatic treatment of ICD be followed and the initial dose be individualized, based on the intensity of the patient's pain and the occurrence of adverse events, which may motivate the substitution of one opioid for another. This individualization suggests that the incidence of adverse, refractory or intolerable effects can be reduced and, in result, improve the patients' quality of life [12,16,17].

With the same view, new opioid receptor-antagonist drugs with peripheral effects, such as oxycodone, naloxone and methylnaltrexone, despite having a mechanism of action similar to opioids, eventually present specific differences as for receptor affinity and pharmacodynamics, leading to positive differences in analgesia and reduction of side effects, and may be a substitute alternative to other opioids[11,12,17]. In two studies, a lower tendency to use laxatives was attributed to such drugs[11,17].

In cases of established fecal impaction, the administration of enemas is indicated, regardless of causing pain, discomfort and being difficult to handle, as they promote temporary relief of symptoms and abdominal comfort. It consists in the elimination of impacted stool by means of rectal drug administration or by taking laxatives in high doses orally. However, this maneuver is contraindicated in certain clinical conditions, such as leucopenia, thrombocytopenia, anal lesion or severe immunosuppression, and without the prior consent of the patient[17].

Diet therapy

Just as drug therapy may be essential for the treatment of constipation, in a synergistic way, the incentive to change eating habits, with greater intake of fibers and liquids, can also be helpful in this condition, since they act directly on the functioning of the bowel and stool formation. Nevertheless, in order to achieve success in treatment, dietary guidelines should be explained as clearly as possible, so that patients and/or caregivers minimize possible errors and achieve treatment success[10].

It is a fact that, even under nutritional monitoring, with adequate supply of fluids and food, there are cases difficult or impossible to reverse due to the patient's very condition, such as patients with cachexia, whose intake may be insufficient for normal functioning of intestinal transit and fecal consistency. In such cases, the use of fiber-based nutritional supplements is contraindicated and, as an effective strategy for prevention of constipation, it is recommended to increase the number of meals, with volume of liquids and foods adjusted to the individual tolerance[10].

The impact of health professionals on the treatment

Despite the high incidence, the difficulties related to treatment, and the increase in the number of OIC studies, there is little improvement in health professionals' understanding and communication in regard to the intensity of their patients' symptoms, generating different perceptions of the importance and severity of the disease among the subjects[19]. Four studies have pointed out that OIC and chronic pain are poorly valued or underestimated by health professionals, and that their symptoms receive poor attention, turning themselves to an inadequate treatment[11,14,17,19].

An article evidenced that the average prescription of opioids in Brazil is below the world average consumption, generating an indirect evidence of inadequate pain control in the country[13]. When constipation and pain are underestimated, an obstacle to the management of these conditions is created[14], which may favor the presence of negative behaviors on the part of the patient,

leading them to abandon or reduce the consumption of opioids with the intention of relieving the symptoms of constipation; or, conversely, the pain generated by the discomfort of the absence of bowel movements and abdominal distension may lead them to increase the drug consumption, creating a vicious cycle of intensification of pain and constipation, which could even lead to the creation of a state of acute confusion[11]. On the part of health professionals, such a condition may contribute to a lack of awareness of the impact of the OIC[19].

Limited communication reagarding the symptoms may be related to both subjects. Lack of time and initiative is evidenced among health professionals, as they feel that patients should start the conversation, or by limiting their approach to aspects such as symptoms, laxatives, satisfaction, benefit and the impact of OIC on pain management. On the part of the patients, a lack of clarity regarding the level of symptoms or the omission of IOC symptoms are observed for several reasons, such as fear of not receiving the opioid, lack of understanding of the opioid-constipation relation, and the belief that constipation is a self-care condition, being often considered a constraint and kept non-shared[19].

In another study, it was observed that, when health professionals are attentive to the diagnosis, follow-up and treatment of constipation, it results in better adherence to the recommended laxatives, interfering positively in the management of the disease[17]. Thus, aiming to reduce this problem, clinical education and coordination of care related to OIC management should be promoted among health professionals, in addition to an incentive to a more proactive posture during prevention, in which the communication about constipation is facilitated among the subjects since the onset of opioid treatment, making the patients commited to their own pain management, in order to avoid this condition[19].

CONCLUSION

Through this study it was possible to verify the impact of OIC in all its aspects: diagnosis of the symptoms, risk factors related to the onset of the condition, involvement in cancer pain treatment, as well as the modalities of existing treatments. Moreover, the disagreements between the patients' and the health professionals' perceptions of care were demonstrated, showing the existence of communication problems that can have negative repercussions in the treatment of the condition.

It is important that OIC be managed to provide abdominal comfort and self-care in patients, with a consequent reduction in treatment costs. To this end, it is necessary to train health professionals, prevention related to risk factor management, and periodic follow-up, in addition to the early onset of diet therapy (with dietary guidelines and encouragement to changes in eating habits) and drug therapy (with opioids prescribing adjusted according to changes in pain or adverse effects in the patient, and encouragement to the use of laxatives).

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