Management of Persistent Hiccups in a Palliative Care Patient: A Brief Review through an Illustrative Case Report

Tratamento de Soluços Persistentes num Doente Paliativo: Uma Breve Revisão através de um Caso Clínico Ilustrativo

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ABSTRACT

Hiccups are a very uncomfortable experience for palliative care patients and can greatly impact their quality of life.

Physical manoeuvres can often terminate acute hiccups. Persistent and intractable hiccups that continue for days or months are rare and difficult to treat. In situations where no reversible cause is identified, or where physical manoeuvres have failed, a systematic approach is required.

The causes of hiccups may be divided into central and peripheral types. The drugs of choice for central causes of persistent hiccups are baclofen and gabapentin as an alternative, with metoclopramide recommended as the first choice for peripheral causes.

The management of persistent hiccups presents a clinical challenge requiring further research on pathophysiology and treatment strategies. With this case report we provide a brief overview of the causes and treatment of this condition.

KEYWORDS: Hiccup; Palliative Care

RESUMO

Os soluços são uma experiência muito desconfortável para os doentes em cuidados paliativos, podendo influenciar muito a sua qualidade de vida.

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As manobras físicas podem controlar os soluços que surgem de forma aguda. Soluços persistentes durante dias a meses são raros e podem ser difíceis de tratar. Quando nenhuma causa reversível é identificada ou as manobras físicas falham, é importante uma abordagem sistemática.

As causas podem dividir-se em centrais e periféricas. Os fármacos de primeira linha para tratar os soluços de causa central são o baclofeno e a gabapentina como alternativa. A metoclopramida é a primeira linha para o tratamento dos soluços de causa periférica.

O tratamento de soluços persistentes apresenta um desafio clínico que requer maior investigação. Através deste caso clínico fornecemos uma breve revisão das causas e tratamento desta condição.

PALAVRAS-CHAVE: Cuidados Paliativos; Soluços

INTRODUCTION

A hiccup is an involuntary spastic contraction of the diaphragm and intercostal muscles leading to inspiration of air, followed by quick closure of the vocal folds. The physiological mechanism remains unclear, involving the hiccup "reflex arch" (with afferent limb, central mediator, and efferent limb). The afferent limb is believed to include the vagus, phrenic, and sympathetic nerves, and the efferent limb is mediated through the phrenic nerve to the diaphragm.[1]

The frequency and the duration can be variable. Hiccups are considered persistent if they last more than 48 hours, and intractable if they last more than a month. Hiccups are more common in children, adult males, and in those with comorbid conditions.[2]

The causes of hiccups may be divided into central and peripheral (Table 1). The establishment of the cause is important for the choice of therapy.

The most common causes are peripheral, including gastrointestinal conditions (such as gastro-oesophageal reflux disease, hernia, malignancy, peptic ulcer disease, gastroparesis) and non-gastrointestinal conditions (such as myocardial infarction, pericarditis, aortic aneurysm, bronchitis, pneumonia, asthma, tuberculosis, otitis, and other opportunistic infections in immunocompromised patients). Peripheral causes are thought to cause hiccups by irritation of the phrenic or vagus nerve.[3]

Central causes may include neurological disorders (stroke, brain tumors, encephalitis), infection, trauma, metabolic conditions (uraemia, hyponatraemia, hypercalcemia), psychogenic factors (stress, anxiety, hysteria), and medication (opioids, steroids) amongst others.

The prevalence of hiccups in palliative care patients is unknown. Most hiccups are self-limited. However, 1% to 9% of patients with advanced cancer complain of persistent or intractable hiccups.[3] In these populations the presence of hiccups can be very uncomfortable and can have a profound impact on their quality of life. In some cases, despite extensive investigation, the cause remains unknown, so the focus should be on relieving symptoms.[4]

On the other hand, some of the medications used in a palliative care setting (opioids, benzodiazepines, dexamethasone, dopamine agonists, and chemotherapeutic agents) have also been implicated in their cause and some of them can be used to treat intractable hiccups.[5]

We present a case report aiming to provide some guidance for treating persistent hiccups in the palliative care setting.

CASE REPORT

We present a case of a 56-year-old male, previously autonomous in daily activities, with personal history of gastroesophageal reflux disease, who was diagnosed with locally advanced rectal cancer in June 2023. He underwent primary chemotherapy followed by radiotherapy and long-term chemotherapy. After completing the treatment, in January 2024, disease progres-

TABLE 1. Examples of causes of persistent hiccups in palliative patients.

CENTRAL	
Neurological	Stroke, brain tumors, encephalitis
Non-neurological	Infection, trauma
Peripheral	
Gastrointestinal	Gastro-oesophageal reflux disease, hernia, malignancy, peptic ulcer disease, gastroparesis
Non-gastrointestinal	Myocardial infarction, pericarditis, aortic aneurysm, bronchitis, pneumonia, asthma, tuberculosis, otitis, and other opportunistic infections
Other causes	
Toxic metabolic	Uraemia, hyponatremia, hypercalcemia
Drugs	Opioids, steroids, chemotherapeutic agents
Psychogenic	Stress, anxiety, hysteria

sion was noted locally and with liver, lymph node, and lung metastasis. For this reason, he was proposed for palliative chemotherapy.

At the beginning of May 2023, he was referred to our emergency department with symptoms and signs of bowel obstruction. This was confirmed on the abdominal computed tomography (CT) scan and he underwent derivative emergency surgery with a bypass colostomy due to obstructive rectal cancer. There were no complications during surgery and in the immediate postoperative period. He was admitted to our acute palliative care unit for continuation of care.

He remained under analgesic perfusion with morphine and ketamine for the first 72 hours, steroid therapy (dexamethasone), and gastric protection with a proton pump inhibitor (pantoprazole), with good clinical evolution.

On the third day after surgery, the patient presented with persistent hiccups with progressive worsening. We tried physical maneuvers without response. We then doubled the dose of pantoprazole and started therapy with a prokinetic agent (domperidone) every 8 hours. In the next 24 hours, the hiccups persisted and little response to rescue therapy was observed (first option: oral haloperidol; second option: subcutaneous levomepromazine). On the next day, we added metoclopramide to the continuous morphine infusion. As almost no response was observed, we started oral haloperidol drops every 4 hours and erythromycin every 6 hours.

Due to the maintenance of hiccups, baclofen was started at bedtime on the 5th day after surgery and it was progressively increased up to 30 mg per day.

Nevertheless, hiccups continued and a new therapeutic review was carried out to exclude medical iatrogenesis and an abdominal CT scan was performed to rule out post-surgical complications such as subphrenic abscesses. The CT scan showed disease progression with the increase in hepatic metastases size, the largest one in the right lobe segment, measuring 10 cm x 6cm, and the presence of subphrenic peritoneal carcinomatosis implants.

During these days, subcutaneous levomepromazine and midazolam were used as rescue therapy but with only temporary effects on the hiccups. Even when asleep, our patient had persistent hiccups.

Between the 7th and 8th day after surgery, we stopped haloperidol and started a levomepromazine subcutaneous infusion and oral gabapentin at bedtime. We

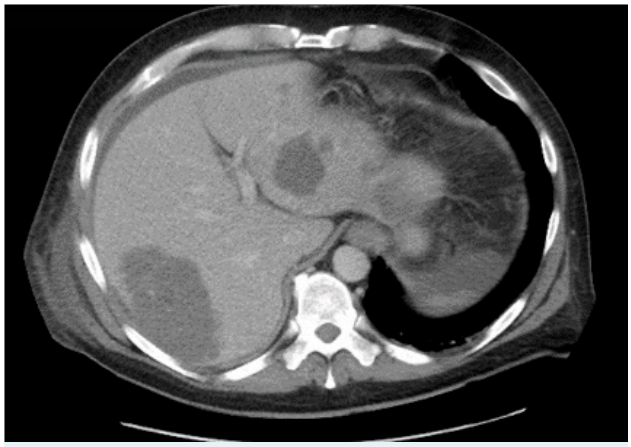

FIGURA 1. Esquema integrado da Consulta de Enfermagem à Distância.

also increased the dose of dexamethasone. As hiccups remained refractory to our treatment, we decided to associate midazolam with the subcutaneous perfusion with subsequent dose adjustment. We reached the maximum dosage of 50 mg of levomepromazine and 30 mg of midazolam per day.

On the 9th day after surgery, the episodes of hiccups started decreasing. The patient kept a moderate level of consciousness and was comfortable.

In the following days, it was possible to progressively reduce pharmacological therapy. On the 16th day after surgery, with 72 hours without evidence of hiccups, erythromycin was suspended and on the 22nd day, levomepromazine and midazolam subcutaneous perfusion were also suspended. Dexamethasone was slowly reduced to the lower dose of 4 mg per day. Baclofen was also reduced and suspended. Gabapentin was maintained, as it was used also as a pain adjuvant therapy.

Until discharge, on the 63rd day after surgery, he did not present any more episodes of hiccups.

DISCUSSION

Persistent hiccups remain a diagnostic and therapeutic challenge and can significantly impact the quality of life of a minority of palliative care patients.

TABLE 2. Pharmacological treatment options for persistent hiccups in palliative care patients.

	First Line	Second Line
Peripheral (gastric)	Proton pump inhibitors, Prokinetic agents	Haloperidol Levomepromazine Midazolam Gabapentin
Peripheral (non gastric)	Baclofen, Gabapentin, Midazolam	
Central	Baclofen	

Non-pharmacological physical manoeuvres should be performed before starting pharmacological therapy. Some of them involve glottic stimulation (holding one's breath, drinking several gulps of water, drinking a glass of water upside down). These manoeuvres are sometimes effective, possibly by stimulating or blocking some of the nerves involved in the hiccups reflex arch.[5] In our patient, non-pharmacological physical manoeuvres were tested but with no success.

Several drugs can be used to treat persistent hiccups in palliative care patients (Table 2).

Many of the options for treating hiccups are based on observational studies, case reports, and small series that do not directly compare treatment options. Most are related to the dopaminergic or GABAergic pathways, which include chlorpromazine, levomepromazine, haloperidol, benzodiazepines, gabapentin, metoclopramide and baclofen.[1]

For the treatment of hiccups secondary to peripheral gastrointestinal causes, it is known that proton pump inhibitors and prokinetic agents like metoclopramide can help.[3,6]

For peripheral non-gastrointestinal pharmacological options, include baclofen, gabapentin, lidocaine, midazolam, methylphenidate and nimodipine.[2]

For hiccups caused by central nervous system lesions, baclofen may be considered a first-line agent, and gabapentin as an alternative. For hiccups refractory to initial treatment, there is no guideline as to how many agents to try singly or in combination. For refractory hiccups, gabapentin has also been used in combination with a proton pump inhibitor, baclofen, or metoclopramide.[6]

Although chlorpromazine has been widely used for that purpose, it is no longer the clear first choice for hiccup treatment, due to the potential for side effects.[4]

If a patient is in the last few days of life, midazolam by subcutaneous infusion is an alternative to relieve intractable hiccups. This general sedation effect was also found to be useful in suppressing hiccup reflexes through case reports.[2]

Our first suspicion in this case was a gastrointestinal cause - worsened oesophageal reflux disease after surgery - in a patient who already suffered from this condition. However, our patient also had other comorbidities and underwent abdominal surgery; therefore, the cause of the hiccups could be multifactorial. We excluded the most frequent metabolic disorders and non-gastrointestinal peripheral causes like pneumonia or myocardial infarction. Our treatment focus was always on relieving symptoms. But, as the treatment options and high doses of drugs failed to relieve the symptoms, we had to search for other possible explanations for the persistent hiccups in our patient. The CT scan showed oncologic disease progression with bigger liver metastases in the right lobe and new subphrenic peritoneal implants, which were probably irritating the diaphragm.

After reviewing and readjusting the medication to these findings, we saw an improvement in symptoms. The increase in the dose of dexamethasone may have contributed to reducing inflammation in both the liver metastasis and the peritoneal carcinomatosis. The sedation effect of midazolam and levomepromazine also suppressed the hiccup reflex in our patient.

There is a lack of evidence in the area of assessment, impact, and treatment of refractory hiccups in palliative care patients due to the rarity of cases. Further studies of persistent hiccups in this setting are needed to create evidence for the elaboration of guidelines. Future research could involve randomized controlled trials comparing levomepromazine, baclofen, metoclopramide, haloperidol, and gabapentin in the management of hiccups.

Our patient's case report illustrates the importance of a correct clinical, physical, and imaging evaluation. It also illustrates the difficulty in assessing and treating palliative care patients for persistent hiccups.

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