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Review

# Challenges in the Diagnosis and Treatment of Hiccup in Neurological Patients

## *Desafios no Diagnóstico e Tratamento de Soluço em Pacientes Neurocríticos*

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***ABSTRACT***

*Hiccup is a prevalent event in the general population and can be found from milder, (so-called benign) to persistent and intractable forms. Hiccups have several causes, but stimulation of the phrenic nerve with compression, deformation and traction are among the most prevalent which could be consequence of mediastinal or lung cancer, gastric and/or esophageal distention, gastroesophageal reflux, instruments (catheters and intubation), cholecystitis, pericarditis or neurological causes. The objective of this paper is to stablish one treatment protocol and hiccup treatment in acute, persistent and intractable stages. A literature review was performed at Scielo, Pubmed, Ebsco, Clin Neuropharmacol, and ScienceDirect databases. Articles and publications from 1970 to 2015 were selected. The relevance of this article is the challenge for diagnostic and the difficulty to stablish the best plan to be addressed in cases of persistent or intractable hiccups in neurological patients, since they probably have many causes.*

***Key words:*** *Hiccup; Protocol; Pathophysiology.*

***RESUMO***

*Soluço é um evento prevalente na população em geral e pode se manifestar desde as formas mais leves (ditas benignas) até as formas persistentes e intratáveis. Diversas são as causas do soluço, porém a estimulação do nervo frênico por compressão, deformação e tração estão entre as mais prevalentes, podendo ser consequência de neoplasias mediastinais ou pulmonares, distensão gástrica e/ou esofágica, refluxo gastroesofágico, instrumentos (cateteres e intubação), colecistite, pericardite ou neurológicas. O objetivo do trabalho é definir e atualizar protocolos de atendimento e tratamento de soluços nas fases aguda, persistente e intratável. Foi realizada uma revisão bibliográfica utilizando base de dados Scielo, Pubmed, Ebsco, Clin Neuropharmacol, e ScienceDirect. Foram selecionados artigos e publicações do período de 1970 a 2015. Propõe-se um protocolo-padrão de atendimento do soluço. A relevância do presente artigo se encontra no desafio do diagnóstico e na dificuldade de definir a melhor conduta frente aos casos de soluços persistentes ou intratáveis em pacientes neurológicos, que provavelmente possuem muitas causas.*

***Palavras-chave:*** *Soluço; Protocolo; Fisiopatologia.*

## Introduction

Hiccup is an involuntary event characterized by intermittent and spasmodic contraction of the diaphragm and intercostal muscles. As a result, there is a sudden inhalation followed by the closure of the glottis producing a characteristic sound. Hiccups can be divided into three categories based on their duration: 1. Attack of hiccups: Episodes that last up to 48 hours; 2. Persistent hiccups: Episodes lasting from 48 hours to one month; 3. Intractable hiccups: Episodes lasting more

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than one month[1]. Similar to burping, hiccups are common and usually occur occasionally. Only when multiple or prolonged episodes occur, it is considered pathological. The medical term for hiccups is singultus. In general, only left unilateral contractions of the diaphragm are involved, but sometimes also on both sides of the diaphragm and intercostal muscles[2]. Hiccups are mediated by a reflex arc consisting of afferent vagal, phrenic and sympathetic nerves; central processing in the brainstem; and efferent signals to the diaphragm and intercostal muscles. An injury or stimulus that depolarizes one of the branches of this reflex arc can cause hiccups[3].

## Diagnosis

Diagnosis of short breath (SOB) can be done through exams, in addition to clinical manifestation: 1. Fluoroscopy of the diaphragm, due to the presence of intra-abdominal disorders associated to chronic and intrathoracic hiccup; 2. Electromyography of the diaphragm, scalene and intercostal muscles, recommended against the sense of presence of pharyngeal globus, and may appear as a result of the unilateral involvement of the diaphragm, whose focus will be to observe the phrenic nerve of the injured side, or bilateral diaphragmatic movement due to an afferent or central origin; 3. Magnetic Resonance Imaging (MRi) to confirm neurovascular compression in midbrain; 4. Laboratory tests such as complete blood count (CBC), chemistry screening, abdominal X-ray, endoscopy and/or chest X-ray, used in case of symptoms affecting body organs[5].

**Pathophysiology**

The most important muscle of respiration is the diaphragm. It consists of a relatively thin muscle, dome-shaped, with lower ribs inserted. It is supplied by the phrenic nerves from the third, fourth and fifth cervical segments. When it contracts, the abdominal contents are forced down and forward, and the vertical dimension of the thoracic cavity is increased. Furthermore, the margins of the ribs are lifted and moved out, causing an increase in the transverse diameter of the chest. The external intercostal muscles connect to the adjacent ribs and are inclined down and forward. When they contract, the ribs are tensioned up and forward, causing lateral and anteroposterior movement in both diameters of the chest. The lateral dimension increases due to the 'bucket-handle' movement of the ribs. The intercostal muscles are supplied by the intercostal nerves that leave the cord at the same level.

Intercostal muscles paralysis alone does not seriously affect the breathing because the diaphragm is very effective. The accessory muscles of inhaling include the scalene muscles that elevate the first two ribs, and sternocleidomastoid, which elevates the sternum. The mechanism of the diaphragm and intercostal muscles together is responsible to generate an increase in thoracic volume and consequent negative pressure, which will contribute to the airflow into the lungs. The exhalation is passive and quiet during normal breathing. The lungs and the chest wall are elastic and tend to return to their resting position, after being actively expanded during inhaling. During exercise and voluntary hyperventilation, expiration becomes active. The most important muscles of expiration are the abdominal wall, including the rectus abdominis, internal and external oblique, and the transversus abdominis muscles. Concerning to breath control, this consists of three basic elements: sensors capture information and feed the central controller in the brain that coordinates the information and, in turn, sends impulses to the effectors (respiratory muscles) that promote ventilation. The sensors comprise the chemical control of respiration and work in order to maintain appropriate concentrations of oxygen, carbon dioxide and hydrogen ions in the tissues. The excess of carbon dioxide or hydrogen ions in blood basically acts directly on the respiratory center, generating large increase in inspiratory and expiratory engines signals to the breathing muscles. The chemosensitive area is bilaterally situated lying 0.2 mm beneath the ventral surface of the medulla.

The respiratory center is composed by various groups of neurons located bilaterally in the medulla and the brainstem pons. This respiratory center is divided into three main groups of neurons: 1. dorsal respiratory, located in the dorsal portion of the medulla, responsible for inhalation; 2. ventral respiratory, located in the ventrolateral part of the medulla, primarily by exhalation; 3. pneumotaxic center, found in the upper dorsal portion of the pons, primarily responsible for the frequency control and respiratory amplitude[6]. The hiccup is characterized by massive inhaling, occurring due to a sudden and repeated involuntary contraction (spasmodic) of the diaphragm and external intercostal muscles, interrupted by a sudden momentary and concomitant closure of the vocal

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folds suspending the air exchange, producing a characteristic hoarse noise. Such noise is explained by a clonic spasm of the diaphragm, passing through the glottis which is narrow, and the simultaneous traction of the larynx causing the abrupt passage of inspiratory air, leading to a contraction along with the noise. This occurs due to the movement of the breathing muscles in an unusual way, which are coordinated by the above spinal center, connecting the upper cervical segments of the spinal cord[7]. The hiccup is a reflex of the normal breathing that triggers a reflex arc that is transmitted by vagus nerve and sensory fibers of the phrenic nerve in his afferent branch, and the motor fibers in his efferent limb, to contract these nerves together[8].

Pathophysiology and central connections of this reflex are not well defined. Reflex arc can be related to phrenic nerve in the sympathetic chain, and vagus nerve and its branches. Hypothetically, the reflex arc has continued in central respiratory cerebellar, by the reticular ascending activated formation and hypothalamus, which act as central mediators and ultimately the nerves of the glottis and intercostal muscles and diaphragm. The hindbrain also participates in this event as part of the bulbar parasympathetic system and lists the efferent fibers composed of the phrenic, vagus and recurrent laryngeal and intercostal nerves between the first and eleventh thoracic vertebrae. The nerve branches of the fifth, sixth and seventh cervical vertebrae and hemidiaphragms, trapezius muscle and glottis are the effectors of the reflex arc, connected to the glossopharyngeal nerve. Vagus and phrenic nerves are related to SOB and sixth to twelfth thoracic sympathetic fibers, and associate hiccup to a variety of intra-abdominal and intrathoracic disorders. The SOB, characterized by a change of respiratory rhythm, does not correspond to a normal physiological phenomenon, but is occasionally determined by spastic contraction of the hemidiaphragm and induced excitation of the phrenic nerve, usually unilateral. These phrenic stimulation are produced by different mechanisms, particularly mechanical, but predominantly compressive and tensile, or phrenic nerve deformation in any part of its path, as in hepatomegaly, gastric distension, tumor compression and / or lymphnode, etc[9].

## Treatment

Treatment depends largely on Hiccup's etiology. As an example, can be mentioned a treatment with a proton pump inhibitor or an H2 blocker, when the gastroesophageal reflux disease is a possible cause of SOB. If no cause can be found the initial treatment is based on physical maneuvers, which are easy to implement and have low risk for the patient. As physical maneuvers, we highlight those that stimulate the nasopharynx or uvula, interrupting the normal respiratory function and stimulating the vagus nerve, since the pharmacological therapy should be initiated when the physical maneuvers fail or do not achieve significant results. A variety of classes of drugs have been used for treatment[10]. As complementary and alternative if hiccups are refractory to physical maneuvers and to drug therapy, acupuncture and hypnosis may be suggested. In several studies acupuncture was effective (among 16 cancer patients, 13 had complete remission). Hypnosis also proved to be effective in some studies and has the advantage of not presenting risks and complications for patients. The surgical approach can be successful in cases refractory to conventional treatments, such as phrenic nerve crush or blockage with a local anesthetic. Patients treated with the implantation of a device that controls the diaphragm excursions by electrical stimulation of the phrenic nerve also had success. On Table 1 the main drugs used on hiccup treatment can be seen.

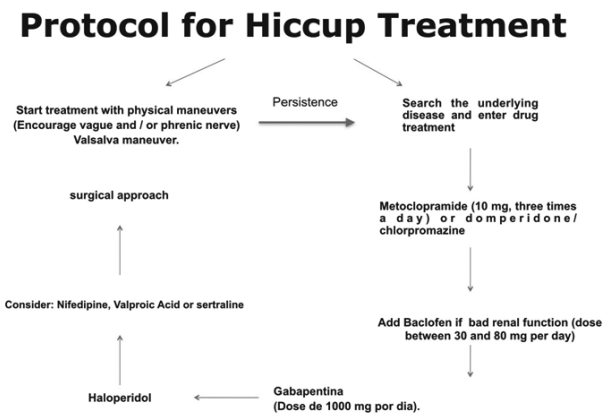
**TABLE 1. Commonly used medicines, mechanisms of action, effects and dosage.**

| Medicine | Mechanism | Adverse effect | Dosage |
|---|---|---|---|
| Chlorpromazine | Antipsychotics, CNS depression | Dystonic reactions and sleep | Initial dose of 25 mg three times a day |
| Metoclopramide | Dopamine antagonist | Fatigue, anxiety and sleep | 10 mg three times a day |
| Baclofen | Relaxing skeletal muscle | Sedation, sleep and respiratory depression | Dose between 30 mg and 80 mg per day |
| Pregabalin | Anticonvulsant Decreases levels of the neurotransmitters in the synaptic clefts | Tremors, dizziness, sleep and respiratory depression | Dose of 150 mg per day |
| Haloperidol | Dopamine antagonist | Fatigue, anxiety and respiratory depression | Initial dose of 0 5 to 2 0 mg two to three times a day |
| Valproic acid | Anticonvulsant Increases the transmissibility of central GABA | Nausea, vomiting and diarrhea | Dose of 10 a 15 mg/kg/day |
| Gabapentin | Anti-epileptic Increases release of GABA | Sleep and sedation | Dose of 1000 mg daily |
| Nifedipine | Calcium channel blockers | Headache and flushing | Doses of 20 mg three times a day |
| Methylphenidate | Inhibition of uptake of dopamine and noradrenaline | Loss of appetite, insomnia, headache and abdominal pain | Doses of 20 a 30 mg daily |
| Midazolam | CNS depressant effect | Related sedatives effects | Dose of 15 mg per day |
| Sertraline | Acting in peripheral serotonine receptors, reducing gastric and esophageal motility | Sweating, tremors, dizziness, dry mouth and diarrhea | Dose of 50 mg per day |

The combination of medication have been reported as successful in improving SOBs. Gabapentin, Baclofen or both have proven to be useful in conjunction with Omeprazole and Cisapride, and the use of all four drugs has also been satisfactory. However, Cisapride is no longer available due to its severe side effects. The advantage of using multiple medications should always be considered and balanced with potential side effects, particularly in a patient population with a high burden of disease and use of various medications[11-15].

Surgical approach is the intrathoracic pacemaker placement in the left hemi-diaphragm. This is placed at the level of the left phrenic nerve, and pericardium, through a minimum thoracotomy. An electrode is connected to a receiver located at the subcutaneous level to control the movements of the diaphragm by electrical stimulation of this nerve[19]. Another surgical procedure is microvascular decompression, through which a suboccipital craniectomy is performed, lateral to the foramen magnum, and incision on the cervical spinal joint. This procedure is used to relieve the pressure on the tenth cranial nerve and medulla[16-19]. Graphic 1 shows a proposed protocol to the treatment of hiccup.

**Graphic 1. Protocol for hiccup treatment**




## Conclusion

The relevance of this article is the challenge for diagnostic and the difficulty to define the best treatment plan to be addressed in cases of persistent or intractable hiccups in neurological patients, since they probably have many causes. This paper shows several types for the diagnosis and their treatment.

## References

1. Amato D. Serotonin in antipsychotic drugs action. Behav Brain Res. 2015;277:125–135.
2. Dobelle WH. Use of breathing pacemakers to suppress intractable hiccups of up to thirteen years duration. ASAIO J. 1999;45: 524-525.
3. Farin A, Chakrabarti I, Giannotta S, Vaynman S, Samudrala S. Microvascular descompression for intractable singultos: Technical Case Report. Neurosurgery. 2008;62(5): E1180-1181.
4. Fibla JJ, Goméz G, Farina C, Estrada G, León C. Colocación de marcapasos diafragmático por toractomía mínima para tratamiento de hipoincoercible. Rev Chilena de Cirugía. 2002;54(5):526-528.
5. Howard RS. Persistent hiccups. BMJ. 1992; 305(6864):1237-1238.
6. Kahrilas PJ, Shi G. Why do we hiccup? Gut. 1997;41(5):712-713.
7. Kolodzik PW, Eilers MA. Hiccups (singultus): review and approach to management. Ann Emerg Med. 1991;20(5):565-573.

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8. Lipps DC, Jabbari B, Mitchell MH, Daigh JD Jr. Nifedipine for intractable hiccups. Neurology. 1990;40(3 Pt 1):531-532.

9. Madanagopolan N. Metoclopramide in hiccup. Curr Med Res Opin. 1975;3(6):371-374.

10. Marinella MA. Diagnosis and management of hiccups in the patient with advanced cancer. J Support Oncol. 2009;7(4):122-127.

11. Maréchal R, Berghmans T, Sculier P. Successful treatment of intractable hiccup with methylphenidate in a lung cancer patient. Support Care Cancer. 2003;11(2):126-128.

12. Martínez Rey C, Villamil Cajoto I. [Hiccup: review of 24 cases]. Rev Med Chil. 2007;135(9):1132-1138.

13. McNally PR. Segredos em Hepato/Gastrenterologia. 1ª ed. Porto Alegre: Artmed; 1999.

14. Pinczower GR. Stop those hiccups! Anesth Analg. 2007;104(1):224.

15. Porzio G, Aielli F, Verna L, Aloisi P, Galletti B, Ficorella C. Gabapentin in the treatment of hiccups in patients with advanced cancer: a 5-year experience. Clin Neuropharmacol. 2010;33(4):179-80. doi: 10.1097/WNF.0b013e3181de8943

16. Ramírez FC, Graham DY. Treatment of intractable hiccup with baclofen: results of a double-blind randomized, controlled, cross-over study. Am J Gastroenterol. 1992; 87 (12): 1789-1791.

17. Regnard C. Dysphagia, dyspepsia and hiccup. In: Hanks G, Cherny NI, Christakis NA, Fallon M, Kaasa S, Portenoy RK (eds). Oxford textbook of palliative medicine. 4th ed. New York, NY: Oxford University Press; 2010. p. 812-832.

18. Theohar C, McKegney FP. Hiccups of psychogenic origin: a case report and review of the literature. Compr Psychiatry. 1970;11(4): 377-384.

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