Vagus nerve stimulation for chronic intractable hiccups

Case report

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Intractable hiccups are debilitating and usually a result of some underlying disease. Initial management includes vagal maneuvers and pharmacotherapy. When hiccups persist despite medical therapy, surgical intervention rarely is pursued. Cases described in the literature cite successful phrenic nerve blockade, crush injury, or percutaneous phrenic nerve pacing. The authors report on a case of intractable hiccups occurring after a posterior fossa stroke. Complete resolution of the spasms has been achieved to date following the placement of a vagus nerve stimulator.

Key Words • hiccup • vagus stimulation • functional neurosurgery

The hiccup is a universal experience that remains poorly understood. It consists of a sudden powerful activation of the inspiratory muscles of the thorax, diaphragm, neck accessory, and external intercostal muscles, with brief inhibition of the expiratory muscles and active movement of the tongue toward the roof of the mouth. Active adduction of the vocal cords follows initiation of the inspiratory flow. The English name “hiccup” as well as the French term “hocquet” is onomatopoeic for the sound caused by forced inspiration against a closed glottis. When hiccups become intractable (that is, singultus), this otherwise benign curiosity can lead to insomnia, wasting, exhaustion, and even death.

Pharmacotherapy is the first approach to treatment. Phrenic nerve blockade or pacing may also be performed in cases not responsive to medication. We describe the case of a patient with intractable hiccups unresponsive to pharmacotherapy or phrenic nerve manipulation, who was successfully treated with vagus nerve stimulation. This stimulation therapy has been used widely in treating patients with seizures whose symptoms are not optimally controlled with antiepileptic medications. The featured case represents the first in which VNS therapy has been used in hiccup treatment.

Case Report

History. Two years prior to his initial presentation in our clinic, this 51-year-old man suffered three successive cerebellar strokes requiring decompressive craniectomy. Approximately 6 months before the first stroke was diagnosed, he began to experience bouts of hiccupping lasting 2 to 5 days separated by periods of up to 2 months. No origin of the strokes was discovered, and the patient was prophylactically placed on the anticoagulant Plavix (clopidogrel bisulfate). Immediately following the first stroke, hiccups began occurring for periods lasting up to 1 month. The hiccups occurred continuously for 7 months during wakefulness and sleep with a periodicity of every 4 to 5 seconds. Multiple home remedies as well as recommended medical therapies such as chlorpromazine, metoclopramide, domperidone, papaverine, and baclofen were unsuccessful in alleviating the singultus. Trials of other medications including cyclobenzaprine (Flexeril) and tizanidine (Zanaflex) provided no relief. The patient’s family practitioner prescribed butorphanol tartrate (Stadol) for an unrelated episode of left leg pain, which coincidently relieved the hiccups for approximately 30 minutes. Thereafter, the patient self-administered intramuscular Stadol injections up to 12 times daily to experience short episodes of relief. Self-induced vomiting also produced brief periods without hiccups, lasting approximately 30 minutes.

Examination. After 7 months of chronic intractable hiccups, the patient presented to our neurosurgical clinic for further evaluation and treatment. Initial MR imaging studies of the brain revealed a large zone of encephalomalacia of the left cerebellar hemisphere extending to the vermis inferiorly with some sparing of the superior medial left cerebellar hemisphere (Figs. 1 and 2). Blood chemistries were unremarkable. Fluoroscopic studies of the chest revealed bilateral diaphragm involvement concurrent with hiccupping. A series of peripheral nerve blocks were then performed using fluoroscopy. A right phrenic nerve block with 10 ml 25% mancurin paralyzed the right hemidiaphragm, although the hiccups remained. Ten minutes after the nerve block...
block, hiccups were relieved as the patient’s voice became hoarse. These findings indicated the potential efficacy of a right recurrent laryngeal nerve block together with a right vagus nerve block, which could be achieved by local extension of the paralytic agent. Restoration of nerve function 6 hours later corresponded with the return of right hemidiaphragm function, normal voice, and hiccups. The next day he underwent percutaneous left phrenic nerve pacing, which resulted in no change in diaphragm movement or hiccup occurrence. Subsequently, a left vagus nerve block was administered, which alleviated the hiccups (associated with a hoarse voice) for 45 minutes.

**Treatment.** Based on the successes of the vagus nerve blocks, we decided to implant a peripheral nerve stimulator lead (Medtronic, Minneapolis, MN) to the left vagus nerve, which was externalized for trial stimulation. We chose the left vagus nerve because of the increased incidence of bradycardia on right-sided vagus nerve stimulation compared with left-sided stimulation in animal models. Following surgery, the patient did not hiccup, except for 10 minutes in the immediate postoperative evening. His voice was notably hoarse while the hiccups remained absent. No trial stimulation was applied because the hiccups did not recur while he was observed over the next few days. Three days later, the patient returned to the operating room for removal of the peripheral nerve stimulator leads and placement of VNS leads (Cyberonics, Houston, TX) to the left vagus nerve. The generator powering the VNS leads was not implanted at that time. Because the peripheral nerve stimulator lead was effective in treating hiccups merely on direct contact with the nerve and without stimulation, the physicians and patient agreed to the placement of VNS leads without applying stimulation. The generator could be placed at a later date if the hiccups were to return. Unfortunately, the hiccups returned within 4 hours of surgery; thus the generator was implanted the following day. Hiccups returned several hours after this procedure. On the next morning stimulation was begun with the following initial settings: frequency 15 Hz, pulse width 750 μsec, amplitude 1.5 mA, and delivery 30 seconds every 5 minutes.

Complete relief of hiccups was maintained for the next 10 days. The patient then returned to the outpatient clinic where the intensity of the applied stimulation was increased. This suppressed his hiccups for approximately 30 minutes. When the hiccups returned, the stimulation parameters were again increased and the hiccups stopped. The current automatic settings are 1.75 mA, 20 Hz, and 500 μsec pulse width delivered for 30 seconds every 1.8 minutes. The magnet activation settings are 2 mA for 60 seconds with a pulse width of 750 μsec.

**Postoperative Course.** Subsequently, the patient reports having to use his magnet occasionally (once a week) to activate the vagus nerve stimulator to provide extra stimulation to suppress the hiccups. He has noticed that if he activates the stimulator after only two to three hiccups he experiences an immediate therapeutic response, whereas if he waits longer it is usually necessary to activate the stimulator several times. During a 3-month postoperative follow up we conducted a no-stimulation trial; the hiccups returned within 5 minutes of turning off the stimulator, however.

**Discussion**

The hiccup reflex arc is customarily divided into an afferent limb, a central connection, and an efferent limb. The afferent pathways comprise the vagal, phrenic, and sympathetic (T6–12) branches. The efferent pathways constitute the phrenic nerve to the diaphragm, direct plexal branches to the scalene muscles, vagal branches to the glottis, and intercostal nerves to the external intercostal muscles. The central connection is a nonspecific area between the C3–5 spinal levels and the brainstem. The pathophysiological
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disturbance that causes episodic or intractable hiccups usually involves the afferent or efferent neural pathways.\textsuperscript{10,12,18} Brainstem pathology, although distinctly less common, has also been well documented as a central cause of intractable hiccups.\textsuperscript{2,8,11,16,17}

Pharmacotherapy for intractable hiccups includes dopamine antagonists such as chlorpromazine and haloperidol; antiarythmics such as nifedipine, lidocaine, and phenytoin; and other medicines such as metoclopramide, baclofen, and gabapentin.\textsuperscript{2,4,15} Effective surgical management may include phrenic nerve blockade or pacing.\textsuperscript{5,22}

Although the phrenic nerve is believed to be the only motor nerve innervating the diaphragm, an accessory phrenic nerve may supplement it. In these cases, blockade of the phrenic nerve will not produce paralysis of the diaphragm.\textsuperscript{13} Furthermore, hiccups of central origin are associated with bilateral diaphragm contraction; thus unilateral phrenic nerve block in these cases—although it paralyses the ipsilateral diaphragm—is unlikely to relieve hiccups.\textsuperscript{9} Bilateral phrenic nerve blockade may also be ineffective for hiccups of central origin. As mentioned previously, efferent pathways involved in hiccup movement include not only the phrenic nerves, but also the direct plexal branches to the scalene muscles and the intercostal nerves to the external intercostal muscles. Note that a bilateral phrenic nerve blockade is cautioned against because of the risk of compromising pulmonary function. Percutaneous phrenic nerve stimulation has also been reported in treating hiccups.\textsuperscript{14}

In the patient in the present case whose hiccups had a central origin and began following a posterior fossa stroke, administering a phrenic nerve block was effective only when accompanied by a vagus nerve block. An explanation for the success of both the vagus nerve blockade and the application of stimulation might lay in the fact that manipulation of the vagus nerve, which is involved in the afferent limb of the hiccup pathway, disrupts signals leading to a hiccup. Perhaps VNS was effective because of vagal nerve behavior in the presence of cerebellar disease. Two cases of cerebellar disease leading to hiccups have been reported,\textsuperscript{15,16} however, the hiccups were medically intractable in both cases.

Why the phrenic nerve blockade and stimulation were not beneficial in the patient in our case is unknown. Previously mentioned reasons for the failure of phrenic nerve blockade might apply in our case. Perhaps the phrenic nerve—despite its involvement in both the afferent and efferent limbs of the hiccup pathway—does not interfere with signal transmission of hiccups as the vagus nerve does.

Conclusions

Clearly, further studies are needed to determine whether VGS relieves hiccups because of its unique position within the hiccup pathway or because of our patient’s particular underlying pathology.

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References


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