PAIN MEDICINE CASE REPORTS

ISSN 2768-5152

Volume 10, Number 4, pp. 365-368

Peripheral Nerve Stimulation of the Phrenic Nerve for Intractable Hiccups: A Novel use Case Series

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Background: Intractable hiccups are defined as hiccups that persist for more than one month. Although rare, they are often refractory to conventional therapies and can significantly impair quality of life.

Case Report: Our case series describes the use of phrenic nerve peripheral nerve stimulation (PNS) in 2 patients, a 73-year-old man and a 52-year-old man, with chronic intractable hiccups. Medical management and various interventional procedures provided only transient improvement. PNS of the bilateral phrenic nerves resulted in immediate and sustained symptomatic improvement in both patients, as reflected by a decrease in Hiccup Assessment Instrument scores. No complications were observed, and both patients reported significant improvements in quality of life.

Conclusions: These findings highlight the potential role of phrenic nerve PNS as a viable treatment option for patients with intractable hiccups refractory to conventional treatments. Further investigation is warranted to validate these findings and establish its durability of benefit.

Key words: Peripheral nerve stimulation, PNS, neuromodulation, hiccups, case series

BACKGROUND

Chronic, intractable hiccups can progress to a severely debilitating condition with significant morbidity and limited treatment modalities. The hiccup reflex arc encompasses afferent inputs from the phrenic, vagus, and sympathetic nerves to midbrain regions, with efferent outputs to the diaphragm, intercostal muscles, and glottis (1). Disruption of this reflex arc can lead to chronic hiccups, resulting in considerable physical and psychological distress (2).

Management of intractable hiccups is complex, requiring a creative approach beyond standard of care. Since the 1950s, chlorpromazine has remained as the only hiccup treatment approved by the US Food and Drug Administration (3), but recent research suggests that interventional techniques, such as phrenic nerve blocks and targeted vagus nerve stimulation, may hold promise (4-6).

Peripheral nerve stimulation (PNS) has been recognized for its effectiveness in treating persistent pain syndromes (7). While the potential of PNS for treating chronic intractable hiccups remains under investigation, our case series introduces the novel use of phrenic nerve neuromodulation for 2 patients with intractable hiccups, underscoring its significance for clinical application and scientific inquiry.

CASE PRESENTATION 1

A 73-year-old African American man with a history of hypertension, small bowel obstruction secondary to

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Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.
Patient consent for publication: Consent obtained directly from patient(s).
This case report adheres to CARE Guidelines and the CARE Checklist has been provided to the journal editor.
Accepted: 2026-02-04, Published: 2026-06-30

adhesions, chronic kidney disease, gastroesophageal reflux disease, prostate cancer, and congestive heart failure presented with daily intractable hiccups for 6 years without a known precipitating event. The hiccups severely disrupted his quality of life; he could not eat without regurgitating, sleep more than 2-3 hours per night without being woken up, speak normally, or engage in singing, one of his favorite hobbies.

The patient was initially rated as a "moderate" or a 6/10 on the Hiccups Assessment Instrument (HAI), a tool used for subjective assessment of hiccup severity (Figs. 1 and 2). Multimodal conservative management with gabapentin, baclofen, metoclopramide, amitriptyline, orphenadrine, omeprazole, chlorpromazine, and thalidomide was unsuccessful, and his hiccups persisted. Advanced measures, with external vagal nerve stimulation, as well as bilateral phrenic and stellate ganglion blocks, provided only transient relief not greater than 24 hours. The patient agreed to proceed with bilateral phrenic nerve PNS placement under ultrasound guidance, which was completed without any complications.

Immediately following placement of the right lead, the patient had 50% improvement in symptoms, and he was able to speak in full sentences for the first time in 6 years. One month later, the procedure was repeated on the left phrenic nerve. Standard default settings of 100 Hz frequency were used for the bilateral stimulators. The device manufacturers' proprietary device settings for intensity range from 0-100 and do not correspond to any standardized unit of measurement. The left PNS intensity was initially programmed at 15 and averaged between 18-25 during therapy and at explant. The right PNS left the facility at 35 intensity and averaged between 35-42 during therapy and at explant.

The reduction in hiccup severity was accompanied with the patient's renewed ability to speak and sing, resulting in a significant improvement in his quality of life. At the 4-month follow-up, the patient reported

Score	Rating	Description
1-3	Mild	Nagging but cause little interference with activities of daily living
4-6	Moderate	Significantly interfere with activities of daily living
7-10	Severe	Disabling, prevent the performance of activities of daily living

Fig. 1. HAI scoring explanation.
Abbreviation: HAI, Hiccups Assessment Instrument.

	Prior to PNS	2 months	3 months	4 months	6 months	12 months
Case 1	6	2		4		
Case 2	9		7		4	2

Fig. 2. HAI preprocedure and at follow-up.
Abbreviation: HAI, Hiccups Assessment Instrument(s).

an HAI score of 4/10 (Fig. 2). Weeks later, his HAI score returned to a 6/10, and he was treated with 4 mL of 2% nebulized lidocaine, resulting in a 50% improvement in his HAI score to a level of 3/10. He reported continued improvement with mild fluctuations in his speaking ability, especially in comparison to his deficits prior to PNS. No complications were observed throughout the follow-up period.

CASE PRESENTATION 2

A 52-year-old man with a history of hypertension and remote COVID-19 requiring a tracheostomy in 2020 presented in 2023 with 9 months of hiccups. The hiccups would intermittently last for hours and severely impact his quality of life, leading to substantial weight loss from difficulty eating and frequent emesis. The patient rated his hiccup severity as 9/10 on the HAI, scored as "severe" (Figs. 1 and 2). Despite trials with baclofen, omeprazole, cyclobenzaprine, chlorpromazine, diazepam, and acupuncture (8), his symptoms worsened, and bilateral stellate ganglion blocks followed by a cervical epidural steroid injection provided transient relief for 3-6 hours.

Given the refractory nature of his condition, bilateral phrenic PNS leads were implanted under ultrasound guidance and set to the standard 100 Hz frequency. Postprocedure, the patient reported a significant reduction in both the frequency and severity of his hiccups. Twelve-week follow-up assessments revealed sustained improvement in the patient's condition. His HAI score decreased by 22% to 7/10 postoperatively (Fig. 2). He continued to experience improvement in his symptoms, with further reductions in HAI scores to 4 and 2 at the 6- and 12-month follow-up assessments, respectively (Fig. 2). The combined use of phrenic nerve PNS and oral medications, including baclofen, gabapentin, and chlorpromazine, resulted in 4-6 hour hiccup-free intervals throughout the day. Interestingly, he also reported consistent cessation of his hiccup symptoms with exercise or physical activity associated with an increase in heart rate. The average intensities for the left and right PNS during therapy and at explant were 35 and 13, respectively.

DISCUSSION

Hiccups, although common, have a complex and multifaceted pathophysiology. There are several theories: neurotransmitter imbalances (gamma-aminobutyric acid and dopamine), and mechanical or chemical disruptions within the gastrointestinal tract, but they all lead to an

unimpeded and recurring hiccup reflex arc. The current treatment algorithm targets these imbalances with agents, such as chlorpromazine, metoclopramide (dopamine), and benzodiazepines (gamma-aminobutyric acid). The hiccup reflex arc is described in 3 parts: the afferent limb includes the phrenic, vagus, and sympathetic nerves, the central processing unit lies within the midbrain, and then extends to the efferent limb via the motor fibers of the phrenic nerve to the diaphragm and accessory nerves to the intercostal muscles. Despite this insight, the exact location of the lesion along the hiccup reflex arc remains difficult to localize, relying on clinical judgment and patient response. It is no surprise that intractable hiccups remain a debilitating disease that becomes exceedingly difficult to treat.

Vagal nerve stimulation has been explored as a therapeutic modality for hiccups; however, it lacks consistent reproducibility in clinical studies (6,9). Phrenic PNS may offer several advantages: it is minimally invasive, stimulation parameters can be titrated to patient response, and it can be performed under ultrasound, avoiding radiation exposure. Recently, it was proposed that the stimulation of large-diameter fibers within peripheral nerves transmits to nonnociceptive wide-dynamic-range interneurons within the dorsal column (10). In addition to analgesia, the supraspinal and cortical effects of this stimulation may propagate into the modulation of central sensitization, termed as "reconditioning" (10). Similarly, the mechanism by which PNS modulates the reflex arc is unclear. However, given the complex interplay of the afferent-central-efferent limbs of the arc and the rippling effects of PNS that extend proximally from the leads, it may be supposed that this aberrant arc may be reconditioned by PNS.

Irritation of the vagus and phrenic nerves that supply the diaphragm can trigger repeated hiccups, resulting in irritation of the bronchial tree, in turn leading to sudden contraction of the diaphragm. Inhaled lidocaine has been proposed to act directly on the vagus nerve receptors and relax the smooth muscle of the bronchial tree (11). Therefore, inhaled lidocaine may be considered when oral medications are ineffective, or as an adjuvant therapy option following phrenic PNS as demonstrated in our patient.

The potential applications of PNS and inhaled lidocaine can extend beyond chronic hiccups and may have utility in acute care as well. For example, postoperative hiccups are a known phenomenon of thoracic procedures and can pose a serious risk of wound dehiscence (12). There may be a role for PNS in mitigating these risks, and this should be investigated further with standardized outcomes and randomized trials.

It is important to note our conclusions are drawn from observations on a small sample size of 2 patients; thus, a cautious interpretation is advised. Future studies should aim to establish the efficacy of PNS for chronic hiccups with randomized controlled trials. Additionally, proper patient selection and optimization of stimulation parameters are crucial steps for improving outcomes and expanding indications. With more robust investigation, phrenic PNS may be an effective therapy for chronic, intractable hiccups.

CONCLUSIONS

Our case series demonstrates the potential role of phrenic nerve PNS as a therapeutic option for the management of intractable hiccups refractory to conventional therapies. Both patients experienced immediate and sustained reductions in hiccup severity, leading to significant improvements in quality of life. While our findings are promising, continued collaboration and multidisciplinary efforts between all involved providers are necessary to improve our care, deepen our understanding of PNS, and potentially integrate it within the treatment algorithm for intractable hiccups. Further investigation consisting of larger cohorts and controlled trials is warranted to validate the efficacy, safety, and long-term outcomes of this approach.

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