The Laryngoscope

Superior Laryngeal Nerve Block Response Rates in 54 Neurogenic Cough Patients

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Objective: Neurogenic cough related to hypersensitivity of the internal branch of the superior laryngeal nerve (SLN) is often treated with neuromodulating medications, which can cause considerable side effects. An alternative therapy is steroid and local anesthetic injection of the SLN ("SLN block"), initially proposed to benefit those with lateralizing symptoms (tenderness over the thyrohyoid membrane or unilateral cough source). Our objectives are to determine if SLN block produces subjective symptomatic improvements and if repeat injections further improve symptoms, and evaluate clinical factors potentially predictive of response.

Methods: Retrospective chart review of 54 patients receiving SLN blocks at a tertiary medical academic center from January 2010 to June 2020. Medical history and anticipated predictors of positive response, including stigmata of laryngeal hypersensitivity, were recorded. Outcomes included symptomatic response, number of injections required, and side effects. Response was defined subjectively by asking patients whether the injection was beneficial and objectively by using CSI scores.

Results: Fifty-four patients met the inclusion criteria. Thirty-eight patients (70.4%) endorsed improvement. No variables were identified as positive predictors of response. Thirty-two of the 38 (84.2%) endorsed improvement after one injection. Six of 15 (40%) patients who failed the first injection had positive response to the second. No significant side effects were reported.

Conclusion: No localizing symptoms, specific cough features, or aspects of the medical history helped predict response, suggesting that a broader range of patients may be offered the intervention. The majority of patients reported symptomatic improvement and repeat injections may benefit patients with initial nonresponse.

Key Words: chronic cough, Cough/PVFM/Irritable Larynx, neurolaryngology, quality of life, superior laryngeal nerve.

Level of Evidence: 4

***Laryngoscope*, 00:1–7, 2023**

INTRODUCTION

Chronic cough is defined as a cough persisting over 8 weeks,[1] with a worldwide prevalence of up to 12%.[2] Cough is the most common symptom driving ambulatory medical appointments and is associated with significant morbidity.[3] It has numerous potential causes including gastroesophageal reflux disease, upper airway cough syndrome, and cough-variant asthma, but up to 42% of patients[4] have no clear etiology, which may lead to the diagnosis of neurogenic cough. A proposed etiology of this cough is a hypersensitivity of the internal branch of the superior laryngeal nerve (SLN).[5] In some patients with neurogenic cough, digital palpation of the entry point of the SLN through the thyrohyoid membrane can trigger pain or the cough reflex.[6] Neurogenic cough is traditionally considered a diagnosis of exclusion[4,7]; however, some posit that a constellation of normal stroboscopy exam (or a unilateral vocal fold paresis if the motor branch of the SLN is affected)[8]; preceding viral illness, surgery, intubation, or local trauma; and neck hypersensitivity or positional triggers are specific features associated with the diagnosis. Few treatment options are available that provide long-term symptomatic relief, leading to frustration for both patients and providers,[4,9] impairment in usual daily activities[9] and psychosocial functioning,[9] and increased levels of anxiety and depression in refractory cough patients.[10] In addition to speech therapy, the current mainstay of treatment includes neuromodulating medications that may have intolerable side effects or be prohibitively expensive.[11,12]

The current treatment options for neurogenic cough include both pharmacologic and nonpharmacologic interventions.[7] Pharmacologic interventions found to improve patient cough-related quality of life include neural inhibitors such as tricyclic antidepressants,[7,13] gabapentin,[7,13] pregabalin,[7,13] tramadol,[14] and baclofen.[13] Unfortunately, the current pharmacologic treatments can be

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Editor's Note: This Manuscript was accepted for publication on January 02, 2023.

Accepted as an oral presentation at AAO-HNSF 2021 Annual Meeting and OTO Experience, October 3–6 2021, Los Angeles, California, United States.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.30570

prohibitively expensive, require patient adherence, often have side effects, and may require titration.[6,13]

The most well-established non-pharmacologic treatment for neurogenic cough includes cough suppressive therapy with a speech and language pathologist. This therapy has been shown to improve patient cough-related quality of life,[15,16] but these interventions are often limited by cost, patient access to a therapist, and necessity of regular visits.[6,7]

A recently emerging therapy that may be a more convenient option for patients is SLN block with local anesthetic and long-acting corticosteroid. Promising data from early retrospective studies demonstrate that this treatment may improve Cough Severity Index (CSI)[6,17,18] and Hull Airway Reflux Questionnaire (HARQ)[19] scores. This therapy has several potential advantages including low cost and a mild side effect profile.[17] Research on this treatment includes only a small number of retrospective cohort studies[17–19] and case reports[6] primarily measuring objective impact through CSI and HARQ scores. It lacks robust insight into which factors predicted positive response to nerve block and whether success could be expected with additional SLN block after initial non-response.

We hypothesize that SLN block is associated with improved cough in a significant number of patients with a low side-effect profile. The current study has three objectives: to extend the current extant research by analyzing qualitative patient response, to identify patient factors that could predict a positive response to SLN block, and to determine whether there is utility in repeating the SLN block when initially unsuccessful.

METHODS

A retrospective analysis of patients who received SLN block was performed under approval by the Institutional Review Board of a tertiary academic hospital. Participants included all patients who received SLN block between the years of 2010 and 2020 at a single institution. Patients were identified by the Current Procedural Terminology code 64408 for Introduction/injection of anesthetic agent (nerve block), diagnostic or therapeutic procedures on the somatic nerves, or 64450 for Injection(s), anesthetic agent(s), and/or steroid; other peripheral nerve or branch. Patients were excluded if follow-up data was incomplete or if they received the SLN block for a diagnosis other than neurogenic cough.

SLN blocks were performed according to the protocol described by Simpson et al.[17] Two milliliters of a 1:1 solution of triamcinolone (40 mg/mL) and 1% lidocaine with 1:100,000 epinephrine was injected using a 30-gauge needle. Injection was performed where the internal branch of the SLN enters the thyrohyoid membrane, using the superior thyroid tubercle and the greater horn of the hyoid bone as landmarks. In patients who reported pain, globus, or lateralization of cough, the first injection took place on the affected side. If partial or absent response was reported after 2 weeks, a second injection was offered. Patients with persistent lateralizing symptoms received the second injection on the corresponding side, whereas those with midline, bilateral, or poorly-localized symptoms received the injection on the contralateral side.

Electronic medical record review included patient demographic information, medical history (asthma, gastroesophageal/laryngopharyngeal reflux, previous intubations), history of present illness (laterality, duration, globus sensation), diagnostic workup (physical exam, laryngoscopy findings), injection information (number, laterality, and time interval between injections), and patient outcomes data (adverse effects, CSI scores, subjective improvement, and length of follow-up). Unilateral cough source refers to a patient-reported unilateral sensation in the neck identified as the source or trigger of the cough. Trauma was defined as a history of intubation or other neck trauma immediately preceding onset of cough symptoms.

The CSI is a validated measure of cough-related quality of life, with 10 questions rated on a Likert scale from 0–4, with the maximum score of 40 indicating severe symptoms.[20] Importantly, many CSI survey questions rely on social interactions that have been limited to varying degrees by the COVID−19 pandemic, and no minimal clinically-important difference (MCID) has been defined to establish clinical importance of this outcome.[20] Patients filled out a CSI questionnaire immediately prior to receiving an injection and 2 weeks later were given a second questionnaire either via phone, electronic messaging, or at the first post-injection office visit. Post-injection CSI scores received outside of the 14–30 day post-injection window were discarded. Patients were also asked if they perceived a qualitative improvement in cough symptoms separately from CSI data. Patients who endorsed perceived benefit were defined as "responders" and those who denied it were defined as "non-responders."

Analysis of CSI scores between responders and non-responders was performed on Microsoft Excel using two-tailed student's *t*-test, and the confidence interval for response to a second injection was determined using the modified Wald's test.

TABLE I.
Cohort Demographic Data.

Demographic group	Count (%)
Age	59.1 ± 13.9 years
Sex	
Male	14 (26)
Female	40 (74)
Race	
White	47 (87)
African American/Black	4 (7)
Asian other	3 (6)
Duration of cough	
Average	70.2 months
Range	3–480 months

Note: Data is reported as means or raw counts with percentages.

RESULTS

A total of 87 patients were identified with our search query. Eleven were excluded for indications other than cough. Sixty-five replied to questions about whether they noticed qualitative benefit from the injection. Thirty-four completed the CSI survey both before and after the injection. Patients received an average of 2.13 injections, median follow-up was 39 days and 34% completed CSI within the 14–30 day interval. All but two patients began with one unilateral injection. Seventy-one percent of patients who got repeat injections within a month alternated sides; 21% repeated the same side and 7% followed

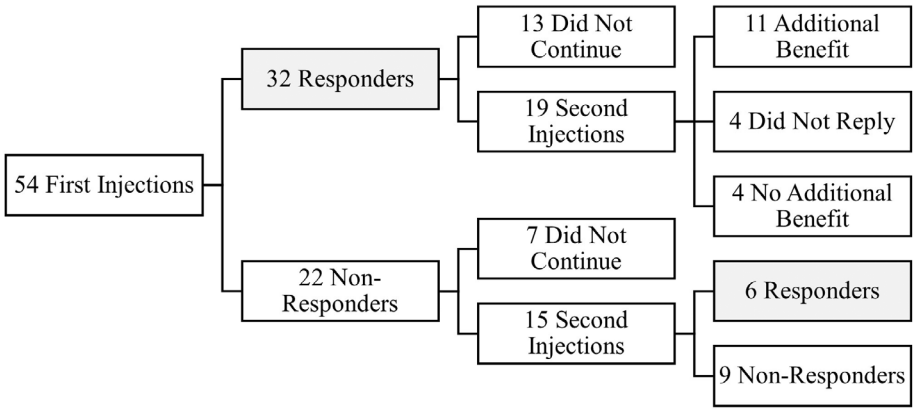

Fig. 1. Qualitative responses to superior laryngeal nerve block injections for neurogenic cough. Patients were asked to indicate "yes" or "no" in addition to the standard CSI score. Shaded boxes indicate responders.

the first unilateral injection with a bilateral injection. Demographic information is presented in Table I.

Of the 54 patients who answered qualitative questions about perceived improvement, 38 (70.4%) reported an improvement in quality of life after the injection ("responders"), and 16 (29.6%) reported no noticeable benefit ("non-responders") (Figure 1). Thirty-two of the 38 total responders (84.2%) reported improvement after just one injection. Nineteen of these patients continued with a second injection, and 11 of the 15 who replied (73.3%) endorsed further benefit. Twenty-two patients did not respond to the first injection. Fifteen of these proceeded with a second injection, and six of those 15 (40%, 95% CI 19.8%–64.3%) responded well to the second. Among non-responders, CSI scores averaged an increase of 1.86 (range −1 to +7), whereas responders averaged a decrease of 1.33 (range −38 to +9) ($p = 0.406$) (Table II). Table III reports data regarding injection laterality and repeat injections.

Of the patient demographic and diagnostic factors reviewed as possible predictors of response to injection, none of the symptoms traditionally associated with a neurogenic cough predicted a greater likelihood of improvement with the SLN block (Table IV). Only concurrent neuromodulator use was associated with differential response rates, specifically decreased response to the injection (52% vs. 89% without neuromodulators, $p = 0.003$). Table IV lists all predictive factors that were investigated.

TABLE II.
Individual Participant CSI Data.

Study number	Subjective response	Injection number	Pre-injection CSI	Post-injection CSI	Change in CSI	Follow-up time (Days)
1	No	1	30	29	−1	26
	No	2	29	29	0	30
5	No	1	34	35	1	15
18	No	1	25	26	1	21
	No	2	26	26	0	28
20	No	1	31	36	5	22
42	No	1	9	16	7	18
15	Yes	1	38	0	−38	29
19	Yes	3	32	32	0	14
	Yes	4	32	34	2	26
21	Yes	1	1	0	−1	20
41	Yes	1	31	34	3	17
50	Yes	2	31	40	9	15
52	Yes	1	19	24	5	19
53	Yes	1	22	25	3	14
68	Yes	3	9	17	8	27
	Yes	4	17	15	−2	24
80	Yes	2	3	4	1	14
	Yes	3	6	0	−6	21

Note: Data includes only those with complete data, defined as a pre-injection CSI score and a corresponding post-injection CSI score within 14–30 days of injections.

TABLE III.
Repeat Injection Data.

		Number	Percent	Percent responders
Laterality: first injection	Unilateral	52	96.3	71.1
	Bilateral	2	3.7	50.0
Laterality: second injection	Ipsilateral	6	21.4	83.3
	Contralateral	20	71.4	80.0
	Bilateral	2	7.1	50.0
Injection interval	Within 2 weeks	15	21.7	73.3
	Within 40 days	41	59.4	70.7
	Over 40 days	28	40.6	89.3
Median injection interval	Non-responders	24 days		
	Responders	37.5 days		

Note: Laterality of each patient's first injection, relative laterality of second injections, and intervals between repeat injections. Median injection interval was not statistically significant ($p = 0.27$). Notably, injection intervals over 40 days were dominated by patients returning several months to years later after initial benefit had faded.

TABLE IV.
Impact of History and Physical Exam on CSI Change.

	Variable	Category	Number of patients	Number of responders	Percent responders	*p*-value
History	Sex	Females	40	28	70.0	0.919
		Males	14	10	71.4	
	Viral infection	Absent	36	26	72.2	0.673
		Present	18	12	66.7	
	GERD	Absent	5	5	100	0.128
		Present	49	33	67.4	
	Asthma	Absent	31	21	67.7	0.623
		Present	23	17	73.9	
	Trauma	Absent	36	26	72.2	0.673
		Present	18	12	66.7	
Exam	Cough source	Unilateral	15	11	73.3	0.674
		Bilateral or midline	24	19	79.2	
	Tenderness to palpation	Absent	8	5	62.5	0.729
		Present	29	20	69.0	
	Laryngopharyngeal reflux	Absent	21	17	81.0	0.174
		Present	33	21	63.6	
	Globus sensation	Absent	39	25	64.1	0.104
		Present	15	13	86.7	
	Laryngoscopy findings	Normal	22	16	72.7	0.753
		Abnormal	32	22	68.8	
	Vocal fold pathology	Absent	44	33	75.0	0.118
		Present	10	5	50.0	
Injection	Post-injection numbness	Absent	37	28	75.7	0.208
		Present	17	10	58.8	
	Post-injection pain or cough	Absent	48	34	70.8	0.833
		Present	6	4	66.7	
	Injection laterality	Unilateral	30	21	70.0	0.947
		Bilateral	24	17	70.8	
	Simultaneous neuromodulator	Absent	27	24	88.9	0.003
		Present	27	14	51.9	

Note: Aspects of history and physical exam and associated responses to SLN block injection. Data reported are percent of each subgroup reporting subjective benefit (i.e. responders). Qualitative benefit significance was calculated using Chi-square test. Some variables were difficult to elicit from chart review and therefore do not include all 54 patients. TTP, tenderness to palpation over the thyrohyoid region; GERD, gastroesophageal reflux disease. LPR, laryngopharyngeal reflux disease. Unilateral injections refers to patients who received one or more injections all on the same side of the neck. Vocal fold pathology refers to atrophy or motion abnormalities on stroboscopy.

All reported side effects of injection were mild, and no patients cited adverse reaction as reason for refusal of subsequent injection. Seventeen patients (31.5%) reported numbness or otherwise altered sensation in the thyrohyoid region immediately after injection, four (7.4%) reported transient throat pain at the site of injection, two (3.7%) experienced brief coughing episodes immediately after injection and one (1.1%) reported mild self-limited laryngospasm. None of these factors predicted response to injection (Table IV).

DISCUSSION

In this study, it was hypothesized that SLN block could be an effective treatment alternative for chronic neurogenic cough. Results demonstrated that SLN block was associated with an improvement in patient-reported quality of life for over 70% of patients, supporting previous literature. In addition, this data did not support any previously suspected or reported predictors of response to the injection, although neuromodulator therapy may be associated with decreased perceived improvement. We also verify the utility of trialing repeat injection after an ineffective first injection, with a 40% response rate. Finally, our data suggest that immediate reactions to the injection such as numbness or pain are not predictive of eventual improvement in cough symptoms.

Neurogenic cough is associated with laryngeal hypersensitivity syndrome (LHS),[21] which is a heightened or inappropriate response to swallowing, singing, talking, positional rearrangements[7,17,22] or external laryngeal stimuli such as cold air or perfumes.[21] Several physiologic mechanisms have been proposed to explain SLN hyperexcitability in neurogenic cough, including hypersensitive sensory receptors, elevated neuropeptide mediation of nerve activity, modulation of brainstem reflexes, behavioral maladaptation, and decreased inhibition of afferent nerve activity.[7,23,24] The underlying hypersensitivity of the SLN may increase patient susceptibility to inciting factors such as viral infection, allergies, asthma, gastroesophageal reflux, and mechanical irritation.[7] Peripheral nerve blocks have been demonstrated as effective treatment options for neuropathic pain such as lumbar radiculopathies,[25] phantom leg pain,[25] and pain secondary to peripheral nerve damage,[26] likely through regulation of local inflammatory response and reducing ectopic afferent nerve activity.[26] The exact therapeutic mechanism for SLN blocks in neurogenic cough is not yet established; however, systemic lidocaine has been shown to improve allodynia, hyperalgesia, and neuropathic pain by decreasing expression of inflammatory markers such as TNF-α, IL-1β, and IL-6 in animal models.[27] Therefore, it is possible that the mechanism for symptom relief far outlasting the plasma concentration of local anesthetic is due to the combined anti-inflammatory effects of the injected lidocaine and steroid rather than the direct sodium channel inhibition.

Our finding that SLN block improved chronic cough symptoms as measured by qualitative patient report is consistent with the current literature. All four extant studies of patients receiving SLN blocks reported significant improvements in either CSI[6,17,18] or HARQ[19] scores. These reductions in CSI among patients treated with SLN block were greater than the CSI reductions observed with medical therapies such as tramadol.[16] Admittedly, our reductions in CSI score were more modest than those already published. However, much of this data was collected during the early stages of the COVID-19 pandemic, a time when social interactions central to the CSI survey were limited. In fact, this data suggest a divergence between patient quality of life and CSI scores in the current pandemic. The change in CSI score did not always capture the full benefit. Qualitative response was considered not only a helpful adjunct to the CSI scores, but in many cases a more accurate reflection of the specific effect of the SLN block. For this reason, subjective improvement in cough severity has more frequently been included in cough research since the pandemic.[19,28,29] In addition, the lack of established MCID[20] for CSI yields ambiguity regarding the desired magnitude of CSI change. Therefore, the reported benefit from 70.4% of patients reinforces the extant CSI data suggesting improved quality of life after the SLN block while simultaneously suggesting the need for better means of cough measurement in a post-COVID-19 world.

Notably, in contrast with Duffy et al.,[18] this study showed no statistically significant differences in subjective response to SLN block associated with vocal fold atrophy or motion abnormalities. That series of 13 patients with neurogenic cough supported an association between vocal fold motion abnormality and increased response to SLN block.[18] Although differences in sample size may contribute to the discrepancy, more investigation into this potential association would be beneficial for identifying future patients who would likely benefit.

Neuromodulator therapy had not previously been analyzed as an independent variable relating to qualitative response to SLN block therapy. Our data indicate that patients taking neuromodulator medications were less likely to report qualitative improvement. This result is contradictory to extant data regarding adjuvant therapy for nerve blocks; for example, adjuvant tramadol has been shown to improve onset and duration of relief in brachial plexus blocks.[30] Although the mechanism is unclear, potential explanations include a selection bias in which patients not fully benefitting from neuromodulators more frequently proceed to SLN, redundant mechanisms of multimodal pain control, or potential differences in how the CSI captures a positive response.

This data also suggests the benefit of multiple injections in some patients, an important clinical consideration not previously analyzed. Six of 38 (15.8%) responders required two injections before noticing an improvement in cough, and 40% of those who did not respond to an initial injection did respond to the second. This is consistent with a study of local injection of lidocaine and methylprednisolone for abdominal trigger point pain, which reported that four out of 34 responders (11.8%) required multiple same-site injections to achieve benefit.[31] Furthermore, 11 of 19 (57.9%) patients who responded to the first SLN block reported additional benefit from a second, whereas only four patients (21.1%)

denied additional benefit. Despite the small sample, these findings further suggest potential value in a second injection regardless of response to the first. However, the need for multiple injections for full therapeutic benefit may be a disadvantage, and the desire to limit the amount of steroid injected to a single site over time may further limit implementation. Repeated injections may make SLN block less appealing for individuals with aversions to needles or longer commutes to appointments. Overall, this data does support trialing a second injection in the appropriate clinical situation.

The SLN block has several advantages over standard treatments such as speech therapy and neuromodulating medications.[15] The CSI changes from SLN blocks reported to this point[6,17,18] were significantly larger than those from either pharmacology or speech-language pathology, which, when directly compared, were found to result in similar improvements in CSI.[16] Furthermore, injections can be performed quickly and safely in an outpatient setting with materials that are easily accessible. Standard neuromodulating treatments risk side effects, significant drug costs, and confusion or noncompliance with medication titration.[12,13] Speech therapy avoids the risk of medication side effects but has its own disadvantages. One established treatment regimen involves four visits with an SLP totaling 195 minutes,[32] which may explain why 76% of chronic cough patients report the number of offices visits being a significant concern.[12] In addition, Medicare patients are responsible for 20% of the cost of each appointment, increasing the financial burden on patients.[33]

Similar to published literature, the adverse effects from SLN block in this study were minor and self-resolving, suggesting that SLN block is a safe option.[6,17–19] An important potential risk factor of SLN block is injection into an artery and retrograde flow to the cerebral circulation, potentially manifesting as confusion, convulsions, respiratory depression, and cardiovascular stimulation or depression.[34] The risk of arterial injection is minimized with experience and by aspiration prior to injection,[35] and it did not occur in this or other studies.[6,17–19] Notably, the majority of patient denied immediate post-injection effects and these were not associated with differential response to injection (Table IV). This may reassure patients and providers who are concerned about injection localization in the absence of immediate effects.

Overall, this study expanded upon previous evaluations of SLN block for neurogenic cough with a larger cohort, broader analysis of factors that might predict a positive response, analysis of repeat injections, and a more direct qualitative assessment of treatment response. However, the patient cohort was still relatively small and lacked placebo control and this study has intrinsic limitations due to its retrospective nature. Furthermore, 22 patients (25.3%) were lost to follow up after initial injection, and the possibility of voluntary response bias in this study cannot be excluded. Many patients only returned to care when their symptoms had returned after temporary alleviation, which drove the limitation of CSI data to the 14–30 day window. Finally, injection protocol among patients included in the study was not standardized, as patients received between 1 and 5 nerve block treatments with inconsistent follow-up. Future research into the value of SLN blocks in neurogenic cough would ideally include prospective trials comparing response to nerve block injection versus placebo or current mainstay pharmacologic treatments. In addition, these authors are performing a prospective study to define several factors that patients commonly inquire about including duration of effect, likelihood of a positive response, variability between injections, and whether cough severity ever returns to baseline. Such a study would eliminate recall bias and collect more accurate follow-up data. Finally, characterization of response to a therapy regimen that combines SLN block and neuromodulators or speech therapy may reveal important interactions.

CONCLUSIONS

A primary aim of this study was to improve medical decision-making and patient counseling. Based on these results, clinicians may now consider SLN block in a broader range of patients, including those who lack localizing symptoms or traditional features of neurogenic cough. When counseling patients, providers can give a better estimation of the likelihood of response; our results indicate that about 2/3 will have a positive response. Patients lacking response after one injection have a 40% chance of responding to a second injection. Lack of immediate numbness or pain after injection has no bearing on likelihood of response. Our institution now frames the injection as a low-risk intervention that is more likely than not to help chronic neurogenic cough. We refrain from giving specific information about length of duration; prospective studies currently underway at our institution may better define this.

ACKNOWLEDGMENTS

The authors acknowledge the work of Bhakthi Deshpande for her work with IRB submission and data retrieval.

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