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Refractory Neurogenic Cough Management: The Non-Inferiority Of Soluble Steroids To Particulate Suspensions For Superior Laryngeal Nerve Blocks

Hisham Abdou

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Refractory Neurogenic Cough Management: The Non-Inferiority of Soluble Steroids to Particulate Suspensions for Superior Laryngeal Nerve Blocks

A Thesis Submitted to The Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by
Hisham Abdou
2024
**Are soluble steroids non-inferior to particulate suspensions for superior laryngeal nerve blocks?**

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**Purpose:** Superior laryngeal nerve (SLN) block utilizing triamcinolone (TA) or methylprednisolone acetate (MP) has been described as an efficacious treatment for refractory cough (RC). Particulate corticosteroid injection in the neck carries a risk of large-particle embolization and devastating neurologic sequelae in the event of inadvertent intravascular injection. Herein, we compare the efficacy of a soluble steroid (dexamethasone, SS) with particulate steroids (PS) in reducing cough severity in RC-patients.

**Materials and Methods:** Patient charts for those receiving SLN blocks by fellowship-trained laryngologists for the sole indication of RC were reviewed. Drug/dose, timing/laterality, and adjuvant treatments were compared using chi-squared test. A paired t-test was used to assess post-treatment improvement and a non-inferiority test was performed to compare improvement between two groups.

**Results:** Of 40 patients included, 27 (67.5%) received SS. Patient and treatment characteristics did not significantly differ between the two cohorts. Significant improvement in cough suppression index (ΔCSI) post-treatment was found in both groups (PS, p=0.024; SS, p<0.001); improvement in the SS group was statistically non-inferior (p=0.003) to that in the PS group.

**Conclusions:** Our pilot study is the first to compare steroids in the field of Otolaryngology, specifically as a component of SLN blocks for refractory cough. Herein, we illustrate that
dexamethasone may be a safe alternative to weaker particulate steroids while non-inferior as a treatment for RC. Generalizability is limited by our study’s retrospective study design and small sample size limiting our ability to conduct multivariate analysis and adjust for follow-up time.
Acknowledgements

First and foremost, I would like to thank Dr. Michael Z. Lerner for his relentless guidance and support throughout my research process and for serving as my thesis advisor at Yale School of Medicine. Dr. Lerner’s guidance made it possible for me to develop this project as a thesis and present my findings to a global audience of scientists studying chronic cough around the world.

Next, I would like to mention this work is made possible by the contributions of Dr. Nikita Kohli, Dr. Ofer Wellisch, Dr. Amar H. Sheth and Astrid Hengartner, who were present at every step of the research process to clarify uncertainties and point me in the right direction.

Additionally, I extend my heartfelt appreciation to my parents and friends for their unwavering encouragement throughout my journey in medical school. Their consistent support has been instrumental in my personal growth and academic achievements.
# Table of Contents

**Introduction** ......................................................................................................................... 1

*Cough Definition* ......................................................................................................................... 1

*The History of Cough* .................................................................................................................... 1

*Acute Vs. Chronic Cough* ............................................................................................................ 2

*Epidemiology of Chronic Cough* ................................................................................................. 2

*Types of Chronic Cough* ............................................................................................................. 3

*The Neurobiology of The Cough Reflex* ...................................................................................... 4

*Role of the Superior Laryngeal Nerve (SLN) in Chronic Cough* .............................................. 7

*Neurogenic Cough Treatments* .................................................................................................. 7

  *GABA Analogs* .......................................................................................................................... 8
  
  *Amitriptyline* ............................................................................................................................ 8
  
  *Other Medications* ................................................................................................................... 9
  
  *Nonpharmacological Treatments* ............................................................................................ 9

*Cough Severity Index (CSI)* ......................................................................................................... 11

*SLN Block for the Treatment of Refractory Cough* ................................................................ 13
Use of Nerve Blocks Within the Anesthesia World ........................................... 13

Steroids Used in Nerve Blocks ........................................................................... 14

Risks Associated with Nerve Blocks .................................................................. 15

Statement of purpose .......................................................................................... 15

Methods ............................................................................................................. 16

Student Contributions ......................................................................................... 16

Ethics Statement and Human Subjects Research ............................................. 17

Procedure ........................................................................................................... 17

Patient Cohort and Data Collection ................................................................. 18

Statistical Analysis ............................................................................................. 19

Results ............................................................................................................... 19

Discussion .......................................................................................................... 26

Limitations .......................................................................................................... 28

Dissemination of Findings .................................................................................. 28

Academic Conferences ....................................................................................... 28

Manuscript Submission ....................................................................................... 29
Conclusion: .................................................................29

References ...............................................................31
Introduction

Cough Definition

Cough is a sudden expulsion of air from the lungs through the mouth, typically accompanied by a distinctive sound. Coughing may happen intentionally or as a reaction to airway irritation, encompassing both reflexive and non-reflexive (behavioral) actions. During illness, coughing may intensify, become unproductive, and overly sensitive, triggered by stimuli that typically would not provoke coughing.¹

While coughing involves coordinated respiratory muscle activity, its control mechanisms rely on intricate neurophysiological processes. In recent years, extensive research has focused on the neural pathways governing coughing, leading to a better understanding of the generation of both voluntary and induced cough.²

The History of Cough

The history of chronic cough as a medical concern dates back centuries. Cough has been documented as a symptom across various historical medical texts and writings, often considered a manifestation of underlying illnesses rather than a distinct condition in itself.³

Throughout history, chronic cough was commonly associated with infectious diseases like tuberculosis, pneumonia, and bronchitis. The understanding of cough evolved with medical advancements, especially during the 19th and 20th centuries, when the focus shifted towards categorizing cough based on its duration and underlying causes.³
In the early 20th century, the differentiation between acute and chronic cough gained prominence, with chronic cough being defined as lasting for weeks or months, indicating a persistent underlying condition. Medical literature started to address chronic cough as a specific concern, distinct from acute episodes.4

Over time, research and clinical studies have expanded our comprehension of chronic cough, leading to the recognition of various conditions contributing to its persistence, including asthma, gastroesophageal reflux disease (GERD), chronic obstructive pulmonary disease (COPD), and upper airway syndromes, among others.5

**Acute Vs. Chronic Cough**

Cough is categorized into acute and chronic based on its duration. An acute cough, lasting less than 3 weeks, is typically short-lived and often linked to upper respiratory infections. On the other hand, a cough persisting beyond 8 weeks is termed chronic cough. While supportive measures may suffice for the self-limited acute cough, managing chronic cough, lasting for months or even years, often presents a significant challenge due to clinicians’ inadequate understanding of the underlying physiological mechanisms and the lack of effective treatments to alleviate it.1,6

**Epidemiology of Chronic Cough**

Cough prevalence spans a significant spectrum within communities, estimated between 2.3% to 18% in the adult population.5,7 In respiratory outpatient settings, chronic cough
prevalence varies widely, ranging from 10% to 38%. A comprehensive meta-analysis reported a general population chronic cough prevalence of 9.6%, defined as a cough lasting longer than three months, with regional disparities; higher rates were observed in Europe (12.7%), Oceania (18.1%), and America (11.0%) compared to lower rates in Asia (4.4%) and Africa (2.3%). Notably, this analysis faced limitations due to varied definitions of chronic cough among studies.

Further studies reported varying community cough prevalence: 5.5% to 13.1% in Europe, 7.3% to 13.6% in Australasia, 2% to 11% in the United States, and 1.6% to 14.1% in the United Kingdom. Cough holds substantial prominence in specialized cough clinics, accounting for 10% to 38% of clinic attendees in the UK and US. Moreover, it serves as the primary reason for visits in general medical practice, representing 6% of encounters in Australia and the US.

Moreover, Cough ranks as the fifth most frequent concern encountered in medical offices, leading to an annual expenditure of $600 million on both prescription and over-the-counter medications, and prompting approximately 30 million office visits every year.

Types of Chronic Cough

Chronic cough manifests in distinct types based on its association with treatable conditions and their impact on resolving the cough. One type involves a cough persisting alongside treatable conditions like asthma, gastroesophageal reflux disease (GERD), and upper airway syndrome, where the cough tends to resolve upon successful treatment of these underlying issues. Other well-described etiologies of chronic cough include ACE-inhibitor-induced, irritant-induced, and other forms of pulmonary disease. Up of 40% of cases, despite a
negative medical workup and non-response to empiric therapies, patients continue to suffer from chronic cough. There are a variety of theories and terminologies employed to explain the symptom of refractory chronic cough. Refractory chronic cough is sometimes termed “cough hypersensitivity syndrome,” encompassing individuals displaying an amplified cough reflex seemingly triggered by innocuous or non-noxious stimuli. Additional somewhat synonymous terms used to describe a refractory chronic cough include “Neurogenic Cough” or “Neuropathic Cough”.

It is important to note, that regardless of the term used, cough hypersensitivity syndrome, neurogenic cough, neuropathic cough, and irritable larynx are considered diagnoses of exclusion which should only be entertained after the completion of an exhaustive negative workup.

No matter the exact pathophysiology of the chronic cough, if the cough continues despite treatment based on guidelines, it can be simply termed refractory cough (RC).

The Neurobiology of The Cough Reflex

Every instance of coughing is the result of a sophisticated reflex arc, initiated by the irritation of cough receptors strategically located in various regions, including the trachea, main carina, branching points of large and smaller airways, and the pharynx. Both laryngeal and tracheobronchial receptors respond to mechanical and chemical stimuli, with chemical receptors sensitive to acid, heat, and capsaicin-like compounds triggering the cough reflex through the activation of the type 1 vanilloid (capsaicin) receptor. Beyond these, additional airway receptors are situated in diverse locations such as the external auditory canals, eardrums, paranasal sinuses, pharynx, diaphragm, pleura, pericardium, and stomach, primarily acting as mechanical receptors stimulated by triggers like touch or displacement.
The sensory fibers in the airways that trigger coughing originate from the vagus nerve, with their endpoints situated within or just beneath the respiratory epithelial lining. These vagal fibers have their cell bodies housed in two separate vagal ganglia, namely the jugular (superior) and nodose (inferior) ganglia. Both ganglia comprise diverse groups of sensory neurons, monitoring various physiological and harmful sensory signals. While most of these neurons exhibit multiple sensitivities, there are distinct subsets specializing in detecting either chemical cues (referred to as chemoreceptor fibers or nociceptors) or mechanical stimuli (known as low-threshold mechanoreceptor fibers or cough receptors). These signals are relayed centrally to specific sensory nuclei in the brainstem for initial processing, before being transmitted to the brainstem respiratory pattern generator to prompt the cough motor pattern. Additionally, they reach higher brain regions to facilitate the perception of airway irritation, enabling behavioral adjustments in response to coughing.

In summary the cough reflex arc comprises three main components:

- **Afferent Pathway:** This involves sensory nerve fibers, branches of the vagus nerve, located in the ciliated epithelium of various upper airway regions (pulmonary, auricular, pharyngeal, superior laryngeal, gastric), and cardiac and esophageal branches from the diaphragm. Afferent impulses disperse diffusely to the medulla.

- **Central Pathway (Cough Center):** The central coordinating region for coughing is situated in the upper brain stem and pons.

- **Efferent Pathway:** Impulses from the cough center travel via the vagus, phrenic, and spinal motor nerves to the diaphragm, abdominal wall, and muscles. The nucleus
retroambigualis, through phrenic and other spinal motor nerves, sends impulses to inspiratory and expiratory muscles, while the nucleus ambiguouss, via the laryngeal branches of the vagus, communicates with the larynx.²⁶

Figure 1. The basic cough neural circuitry. Sensory neurons originating from the nodose (depicted in red) and jugular (depicted in green) ganglia of the vagus nerve, which extend to the airways and lungs, exhibit unique patterns of central termination in the brain stem.

From Keller et. al. (2017)²⁷
Role of the Superior Laryngeal Nerve (SLN) in Chronic Cough

The internal branch of the Superior Laryngeal Nerve (SLN) penetrates the thyrohyoid membrane slightly above the superior laryngeal artery. Upon entry, it bifurcates into an upper and lower branch, serving to relay general sensations like pain, touch, and temperature across areas positioned higher than the true vocal folds. The upper branch provides sensory input to regions such as the inferior pharynx, epiglottis, vallecula, and the laryngeal vestibule, while the lower branch caters to the sensory needs of the aryepiglottic folds and the false vocal folds. Neurogenic cough is a diagnosis of exclusion and is often associated with heightened laryngeal sensitivity, believed to result from post-viral neural damage specifically affecting the internal branch of the superior laryngeal nerve (SLN).

Neurogenic Cough Treatments

The objective of treating neurogenic cough primarily focuses on symptom management, without definitive evidence supporting any role in neural remodeling or long-term alterations in the underlying pathophysiology. Similar to patients experiencing other neuralgias, individuals with neurogenic cough often exhibit a trigger response wherein a stimulus induces coughing, akin to pain episodes in individuals with trigeminal or postherpetic neuralgia. Medication categories like GABA Analogs (gabapentin or pregabalin) and tricyclic antidepressants (i.e. amitriptyline), recognized for their efficacy in managing certain neuropathic pain syndromes, are considered as initial medication choices in neurogenic cough management.
GABA Analogs

GABA analogs, like gabapentin and pregabalin, operate by inhibiting the release of neurotransmitters through the blockade of voltage-gated calcium channels, and their efficacy has been assessed in chronic cough treatment. In a randomized, double-blind, placebo-controlled trial comparing gabapentin to placebo, the gabapentin-treated group exhibited improvements in cough-specific quality of life alongside reduced cough frequency and severity. However, these improvements were not sustained upon treatment cessation. Uncontrolled investigations further advocate for gabapentin and pregabalin in neurogenic cough, as observed in studies by Lee and Woo, where patients with indications of motor neuropathy in the recurrent or superior laryngeal nerve demonstrated enhanced treatment responses, thus supporting the neuropathic paradigm of chronic cough.

Amitriptyline

In a randomized control trial carried out by Jeyakumar et al., a comparison between amitriptyline and codeine/guaifenesin found that 86.7% of individuals in the amitriptyline group achieved a ≥50% improvement in their cough, accompanied by significant enhancements in cough-specific quality of life. In contrast, only 7.7% of those in the codeine/guaifenesin group experienced a similar level of improvement. Additionally, several other reports underscored amitriptyline's effectiveness in alleviating cough symptoms. Bastian et al. demonstrated sustained >50% improvement in six out of eight patients even 20 days following the cessation of medication. Furthermore, Norris and Schweinfurth noted a heightened treatment response in patients exhibiting signs of motor neuropathy during laryngeal examinations. Amitriptyline's pharmacological action, involving the inhibition of norepinephrine and serotonin reuptake, is
proposed to potentially raise the sensory threshold of afferent nerve endings, thereby ameliorating the cough reflex.\textsuperscript{30,31}

**Other Medications**

Other pharmacological compounds exhibiting neuromodulating capabilities have displayed potential in the management of neurogenic cough patients. Baclofen, a $\gamma$-aminobutyric acid (GABA) agonist, showcased its efficacy in augmenting the cough threshold to irritants like capsaicin among healthy volunteers.\textsuperscript{42} In two chronic cough patients, a trial of baclofen resulted in decreased cough frequency and severity alongside an elevated cough threshold.\textsuperscript{43} Botulinum toxin, by inhibiting acetylcholine release at presynaptic neuromuscular junctions and reducing neurogenic inflammation via decreased neuropeptide release from C-fiber receptors, may mitigate glottal trauma and cough severity through modifications in both motor and sensory pathways.\textsuperscript{44,45} Case reports indicated the effectiveness of botulinum toxin in managing habit cough in pediatric patients and in adults experiencing medically refractory cough.\textsuperscript{46,47}

**Nonpharmacological Treatments**

Murry et al. observed an enhancement in cough symptoms through respiratory muscle retraining, emphasizing increased engagement of the abdominal musculature during inhalation and reduced force exertion by the oropharyngeal muscles. This improvement was noted after a minimum of two sessions among patients whose cough persisted despite proton pump inhibitor therapy.\textsuperscript{48,49} Another study, employing a randomized, placebo-controlled, single-blinded design with medically refractory chronic cough patients, highlighted significant advancements in the treatment arm (comprising patient education, cough control techniques, vocal hygiene,
counseling), with 88% reporting improved cough compared to only 13% in the placebo group (undergoing healthy lifestyle education).\textsuperscript{50} After four therapy sessions, these refractory cough patients exhibited enhanced cough-specific quality of life, reduced objective cough frequency measured through a cough monitor, lowered cough reflex sensitivity, and heightened cough threshold to capsaicin exposure.\textsuperscript{51}

While both pharmacologic and nonpharmacologic treatments have shown promise in managing neurogenic cough, further investigations are essential to optimize the identification and management of these patients. Standard practice in chronic pain patients involves titrating doses of medications like amitriptyline, gabapentin, and pregabalin every 3 to 7 days, maintaining an adequate drug trial duration of 4 to 8 weeks, with at least 2 weeks at the maximum tolerated dose.\textsuperscript{52} However, the optimal dose, treatment duration, onset of maximum benefit, and relapse rates following drug cessation remain elusive in neurogenic cough patients. Studies comparing individual medications, medication combinations, nonpharmacologic therapies, and their combined approaches may illuminate the most effective management strategies.

In clinical practice, the initial treatment approach should be determined through an informed discussion with the patient. Consideration should encompass medication cost, patient adherence to therapy, associated voice and breathing difficulties, and potential medication side effects.\textsuperscript{29} For medication trials, following the precedent of chronic pain studies and prior medication trials, titrating the dose weekly and maintaining the optimal dose based on symptom improvement for 2 to 3 months represents a reasonable first step.\textsuperscript{52}
Cough Severity Index (CSI)

The Cough Severity Index (CSI) stands as a concise and accessible patient-reported questionnaire, initially crafted by Shembel et al. in 2013. This tool serves the purpose of quantifying the severity of cough specifically related to the upper airway in patients with chronic cough. Offering a comprehensive approach, the CSI addresses various measurable impacts of chronic cough on a patient's health and overall symptom severity, all while prioritizing clinical practicality.

Noteworthy for its brevity, the CSI presents itself as a short, self-administered questionnaire that is not only easy for patients to complete but also straightforward to score. The strength of the CSI lies in its robust statistical foundation, rendering it a reliable tool for assessing the severity of chronic cough. Moreover, the CSI's versatility extends to its applicability as an outcome measure, allowing for the evaluation of improvements between pre- and post-therapy, be it medical management or behavioral treatment.

As demonstrated in the sample questionnaire below, patients are instructed to contemplate the symptoms they may be experiencing and then select the response that best mirrors how frequently they encounter each symptom (0 = never, 1 = almost never, 2 = sometimes, 3 = almost always, 4 = always). Following this, the scores from the ten questions are aggregated to calculate an overall score, providing a comprehensive assessment of the severity of chronic cough symptoms.
## Cough Severity Index (CSI)

This questionnaire helps to measure the effect that your cough may have on your day-to-day life.

These are some symptoms that you may be feeling.

Please answer each question.

Choose the response that indicates how frequently you experience the same symptoms.

<table>
<thead>
<tr>
<th>Situation</th>
<th>Frequency of problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>My cough is worse when I lie down.</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>My coughing problem causes me to restrict my personal and social life.</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>I tend to avoid places because of my cough problem.</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>I feel embarrassed because of my coughing problem.</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>People ask, “What’s wrong?” Because I cough a lot.</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>I run out of air when I cough.</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>My coughing problem affects my voice.</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>My coughing problem limits my physical activity.</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>My coughing problem upsets me.</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>People ask me if I am sick because I cough a lot.</td>
<td>0 1 2 3 4</td>
</tr>
</tbody>
</table>

**TOTAL 10 x 4 = 40 max**

---

**Figure 2.** Cough Severity Index (CSI) questionnaire as proposed by Shembel et al.\(^{33}\)
**SLN Block for the Treatment of Refractory Cough**

Simpson et al. were pioneers in exploring the efficacy of in-office SLN block as a treatment for chronic cough. Their research hypothesized that a nerve block on the internal branch of the SLN could disrupt the signaling pathway responsible for initiating abnormal cough reflexes by altering sensory feedback. Utilizing corticosteroid and local anesthetic injections in-office, they primarily focused on assessing the impact of unilateral nerve blocks on individuals with chronic cough. Subsequently, Dhillon conducted a case series following the same procedure as Simpson et al., further contributing to the literature by investigating the effects of unilateral SLN block in patients not concurrently using oral neuromodulators. This study reaffirmed Simpson et al.’s findings in this specific patient cohort, suggesting the potential use of nerve blocks as an alternative to oral neuromodulators.

**Use of Nerve Blocks Within the Anesthesia World**

Nerve blocks utilizing corticosteroids or local anesthetics represent a widely recognized therapeutic approach within the realm of anesthesia that is usually used for peripheral neuropathies. Epidural steroid injection has been the most frequently administered therapy for patients with disc herniation and spinal canal stenosis since the 1950s.

The prevalent drugs used for lumbar epidural injections consist of injectable particulate or soluble non-particulate steroids, typically administered alongside a local anesthetic. Over time, triamcinolone acetonide, a particulate depot steroid, had been utilized "off label" for epidural steroid injections, showcasing seemingly positive clinical outcomes. Its perceived effectiveness stemmed from larger particle size, allowing prolonged presence in the epidural space compared to soluble preparations.
**Steroids Used in Nerve Blocks**

Various corticosteroid preparations frequently used in nerve blocks exhibit distinct characteristics in terms of particle size, solubility, and aggregation.

Rosenkranz et al. discovered that certain microcrystals of triamcinolone acetonide (Kenalog) measured over 20 μm in diameter, with an average size of 4.5 μm. They suggested that if these microcrystals precipitate intravascularly, they might merge into larger particles substantial enough to block small vessels within the microcirculation.\(^5\) While Derby et al. showed that the particles of dexamethasone had a size of 0.5 μm, significantly smaller compared to red blood cells, approximately five to 10 times less in dimension. These particles displayed solubility in water and exhibited no signs of aggregation.\(^6\) Their research highlighted the variability in betamethasone particle sizes, which generally measure less than 5 μm. However, some tend to form aggregates, surpassing 10 μm in size, notably larger than red blood cells. On the other hand, the particles of methylprednisolone consistently appear smaller than red blood cells and, despite being densely packed, they exhibit no signs of aggregation.\(^6\)

Regarding metabolic activity, dexamethasone demonstrates a quick onset, but a relatively brief duration of action compared to less soluble preparations.\(^6\) This shorter duration has led some clinicians to consider other particulate corticosteroids as potentially more suitable treatment options. However, recent investigations by Dreyfuss et al. examining the comparative effectiveness of particulate and nonparticulate steroids revealed no clinically or statistically significant difference in immediate efficacy.\(^6\)
**Risks Associated with Nerve Blocks**

Epidural steroid injections, incorporating steroids not sanctioned by the US Food and Drug Administration (FDA), are categorized as "off label." The FDA cautioned against the use of triamcinolone acetonide for epidural purposes in 2011, and in 2014, the FDA's safety announcement highlighted rare yet serious adverse events associated with injections into the epidural space, including vision loss, stroke, paralysis, and fatalities. This announcement stemmed from a review of 15 medical literature references and cases reported in the FDA Adverse Event Reporting System (FAERS), predominantly linked to cervical transforaminal epidural injections. Consequently, following this FDA warning, many physicians transitioned from particulate corticosteroid preparations like triamcinolone acetonide to non-particulate corticosteroid preparations for epidural steroid injections.

Anecdotally, there have not been reports of significant complications resulting from the administration of nonparticulate steroids. In contrast, the injection of particulate steroids has been linked to instances of brain and spinal cord infarctions. This association is thought to stem from the particle size in commonly used steroid formulations, which matches or exceeds the diameter of many arteries. Tiso et al. hypothesized that these complications were due to embolism, a view supported by others who highlighted infarctions resulting from particulate steroid emboli as a primary source of complications. Furthermore, it's reasonable to suggest that larger particle sizes could pose a higher risk of obstructing terminal arterioles.

**Statement of purpose**

Chronic cough poses a substantial health burden on individuals, significantly impairing their quality of life and daily functioning. For those grappling with refractory cough (RC), the
relentlessness of coughing episodes often leads to profound discomfort, disrupted sleep, social isolation, and considerable psychological distress. Amidst these challenges, the search for effective treatments becomes paramount. The use of Superior Laryngeal Nerve (SLN) block, employing triamcinolone (TA) or methylprednisolone acetate (MP), has emerged as a promising treatment modality for refractory cough (RC). However, the administration of particulate corticosteroids in the neck region comes with inherent risks, particularly the potential for large-particle embolization and consequential neurologic complications in cases of inadvertent intravascular injection. Given these concerns, this study aims to comprehensively assess and compare the therapeutic efficacy of soluble steroids (specifically dexamethasone, SS) versus particulate steroids (PS) in mitigating cough severity among patients diagnosed with refractory cough. By scrutinizing the comparative effectiveness of these steroid types in SLN block interventions, we seek to discern and elucidate the relative benefits and safety profiles, thereby contributing critical insights into optimizing treatment strategies for this challenging condition.

Methods

Student Contributions

Under the supervision of Dr. Michael Z. Lerner, the student was responsible for multiple pivotal roles throughout this study. Responsibilities encompassed the conception and design of the work, data acquisition, conducting statistical analyses, initial manuscript drafting, thorough analysis and interpretation of gathered data, and meticulous critical revisions to ensure the manuscript's incorporation of significant intellectual content. The rest of the team collectively engaged in various aspects: Amar H. Sheth, Dr. Ofer Wellisch and Dr. Nikita Kohli participated in the conception, design of the study, and critical intellectual revisions of the manuscript. Amar
H. Sheth with Astrid Hengartner also focused on data acquisition and in-depth data analysis, and interpretation.

**Ethics Statement and Human Subjects Research**

Yale School of Medicine Institutional Review Board (IRB) granted approval for this study. Prior to participating, all participants provided written informed consent. The data was stored in systems compliant with HIPAA regulations.

**Procedure**

The SLN block procedures were performed in the clinic setting following the established technique delineated by Simpson et al. With the patient comfortably seated upright in an examination chair a 50:50 solution consisting of either preservative-free particulate steroid (PS) such as triamcinolone acetonide 200mg/5mL or methylprednisolone 80mg/1mL, or preservative-free soluble steroid (SS) like dexamethasone 10mg/1mL combined with a local anesthetic (1% lidocaine with 1:100,000 epinephrine or 0.5% bupivacaine) was injected. This injection was administered at the entry point of the internal branch of the SLN, situated within the posterior thyrohyoid membrane, using a 27-gauge needle. To locate the entry point accurately, landmarks such as the superior thyroid tubercle and the greater horn of the hyoid bone were utilized.

In some patients, a specific area over the thyrohyoid space triggered discomfort or cough upon palpation, known as a trigger point. For these patients, the injection was directed towards this trigger point. For patients lacking such a trigger point, the injection was aimed at the posterior thyrohyoid (TH) membrane. This choice was made to ensure exposure of the nerve to
the injected material along its entire path over the TH membrane, extending from its posterior aspect to its slightly anterior entry point.

When trigger points were identified bilaterally, injections were administered in staged bilateral fashion. In the absence of a trigger point or unilateral symptomatology, one side was selected arbitrarily for the block. Patients unresponsive to the initial block were offered a contralateral SLN block during their subsequent visit after 2 weeks. However, simultaneous bilateral blocks were avoided to prevent potential complications like dysphagia or aspiration, as bilateral blocks might lead to sensory alterations in the pharynx and larynx.

For patients experiencing temporary relief without substantial improvement following the initial block, repeated SLN blocks were considered as needed to address their persistent cough symptoms.²

**Patient Cohort and Data Collection**

To conduct this study, electronic medical records (EMRs) of patients who underwent an SLN block (CPT 64408) for refractory cough (RC) between 2018 and 2023 were meticulously reviewed under an Institutional Review Board (IRB)-approved protocol. The analysis included patients with comprehensive records, encompassing subjective improvement (SI) and the Cough Severity Index (CSI). However, patients with underlying comorbidities that might contribute to their cough were excluded from the study. Prior to the procedure, participating laryngologists ensured that patients were fully informed about the potential risks and benefits associated with each of the two treatment options. The choice between particulate and soluble steroids was offered to the patients, outlining details such as the potential for prolonged treatment effects with
particulate steroids despite the risk of embolization. Demographic data, including age, sex, the type of adjuvant cough suppression therapy, and the duration until follow-up, were gathered during the data collection process.

**Statistical Analysis**

Comparisons between patient/treatment characteristics were performed using $\chi^2$ tests and student’s t-tests, which were outlined in Table 2. The Cough Severity Index (CSI) scores pre- and post-injection were subjected to analysis through a paired t-test. Additionally, the changes in CSI scores across the two groups were examined using a non-inferiority test (non-parametric), employing JMP Pro 17 software for the analysis. The generation of figures was accomplished using GraphPad Prism 9.5.1 software for visual representation and analysis.

**Results**

As shown in Table 1, a total of 40 patients underwent the Superior Laryngeal Nerve (SLN) block procedure for the treatment of chronic cough. Among these patients, 27 received injections containing soluble steroids (SS - dexamethasone), while 13 received injections with particulate steroids (PS - triamcinolone acetate or methylprednisolone). The mean age of the entire cohort was 61.0 years (SD: 11.9), with no statistically significant difference observed between those receiving SS (mean: 61.8 years, SD: 13.1) and PS (mean: 59.3 years, SD: 8.9) injections ($p = 0.538$).

Regarding gender distribution, 30.0% of the total patients were male, with comparable representation between the SS (29.6%) and PS (30.8%) groups, showing no significant disparity ($p = 0.941$). The majority of patients received bilateral injections (65.0% overall), wherein
subsequent injections on the contralateral side were performed at least two weeks after the initial injection. This bilateral approach was consistent between the SS (66.7%) and PS (61.5%) cohorts (p = 0.750).

In terms of adjuvant therapy, a substantial portion of patients utilized neuromodulators (72.5% overall), with similar prevalence noted between the SS (74.1%) and PS (69.2%) groups (p = 0.748). Noteworthy variations were observed in specific neuromodulator usage, including gabapentinoids (27.5% overall) and amitriptyline (30.0% overall), with distinct preferences seen between the SS (40.7% for gabapentinoids, 22.2% for amitriptyline) and PS (0.0% for gabapentinoids, 46.2% for amitriptyline) cohorts.
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
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Abbreviations: SLN: Superior Laryngeal Nerve; F: female; M: male; MP: methylprednisolone; DX: Dexamethasone; TA: triamcinolone acetonide (Kenalog); CSI: Cough Severity Index.
The utilization of adjuvant cough suppression therapy was prevalent across both groups, encompassing 82.5% of the total patients, with a comparable frequency between the SS (85.2%) and PS (76.9%) cohorts (p = 0.519).

Of significance, the median duration of follow-up significantly varied between the groups, with a median of 34 days (IQR: 72) for the SS cohort and 105 days (IQR: 190) for the PS cohort (p = 0.005), indicating notable differences in the post-procedural observation periods between the two steroid types.
### TABLE 2.

Patient and treatment characteristics undergoing Superior Laryngeal Nerve (SLN) block for chronic cough.

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<th>p-value</th>
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<td>n=27</td>
<td>n=13</td>
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<td>Age, years (mean (SD))</td>
<td>61.0 (11.9)</td>
<td>61.8 (13.1)</td>
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<td>Male (%)</td>
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<td>Bilateral(^a)</td>
<td>26 (65.0)</td>
<td>18 (66.7)</td>
<td>8 (61.5)</td>
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<td>Adjuvant Neuromodulator Use</td>
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<td>Gabapentinoid</td>
<td>11 (27.5)</td>
<td>11 (40.7)</td>
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<td>Amitriptyline</td>
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<td>Adjuvant Cough Suppression</td>
<td>33 (82.5)</td>
<td>23 (85.2)</td>
<td>10 (76.9)</td>
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<tr>
<td>Follow-Up Days (Median (IQR))</td>
<td>49 (87)</td>
<td>34 (72)</td>
<td>105 (190)</td>
<td>0.005(^b)</td>
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</table>

Abbreviations: SS: cohort receiving injection with soluble steroids (dexamethasone); PS: cohort receiving injection with particulate steroids (triamcinolone acetate or methylprednisolone).

\(^a\)Block injected on contralateral side ≥2 weeks following first injection.

\(^b\)Nonparametric test (Independent-Samples Median Test).

Moreover, a subjective improvement was reported by 70.0% of the overall cohort. Specifically, 74.1% of those receiving injections with soluble steroids (SS) reported improvement, while 61.5% of the particulate steroid (PS) group indicated a subjective improvement (p = 0.418), demonstrating a trend but not reaching statistical significance.
Figure 3. A) Boxplot illustrating Cough Severity Index (CSI) scores before and after superior laryngeal nerve (SLN) injection for two treatment groups. X-axis delineates particulate (PS) versus soluble steroid groups (SS). Paired t-tests ($\alpha=0.05$) used to test significant difference between CSI score before (grey) and after (white) injection. (B) Violin-plot illustrating distribution of $\Delta$CSI (pre - post). Non-inferiority (one-sided) used to assess non-inferiority of the SS group compared with PS group. Solid line represents median and dotted line represents the 25$^{th}$ and 75$^{th}$ percentile of $\Delta$CSI.

The mean pre-Cough Severity Index (CSI) scores for the entire cohort was 26.45 (SD: 8.54), showcasing similar baseline cough severity between SS (mean: 26.11, SD: 8.82) and PS (mean: 27.15, SD: 8.25) cohorts ($p = 0.723$). After the SLN block procedure and as shown in Figure 3A, the mean post-CSI scores showed a statistically significant improvement across both groups ($p=0.024$ in PS group, and $p<0.001$ in SS group), with an overall mean of 18.65 (SD: 10.93). Notably, the SS group exhibited a mean post-CSI of 17.52 (SD: 10.84), while the PS group showed a mean post-CSI of 21.00 (SD: 11.18). Despite observable trends towards improvement, the differences in post-CSI scores between the SS and PS cohorts did not reach
statistical significance (p = 0.352). Therefore, a noninferiority study was conducted, which found that the improvement in CSI in the SS group is statistically non-inferior (p=0.003) to the improvement found in the PS group.

**Discussion**

Chronic cough poses a considerable toll on individuals, significantly diminishing their quality of life and daily functionality. The relentless nature of coughing episodes in refractory cough (RC) not only induces profound discomfort but also disrupts sleep, fosters social isolation, and triggers considerable psychological distress. In navigating these formidable challenges, the quest for effective treatments becomes imperative. The utilization of the Superior Laryngeal Nerve (SLN) block, employing triamcinolone (TA) or methylprednisolone acetate (MP), emerges as a promising therapeutic avenue for refractory cough (RC). Nevertheless, the administration of particulate corticosteroids in the neck region introduces inherent risks, particularly the potential for large-particle embolization and consequential neurologic complications in cases of inadvertent intravascular injection.\textsuperscript{72,73}

Against this backdrop, our study seeks to comprehensively evaluate the therapeutic efficacy of soluble steroids (specifically dexamethasone, SS) versus particulate steroids (PS) in alleviating cough severity among individuals diagnosed with refractory cough. By closely scrutinizing the comparative effectiveness of these steroid types in SLN block interventions, our aim is to unravel and clarify the relative benefits and safety profiles. It is also worth mentioning that this thesis is the first study to compare the efficacy of non-particulate steroid solutions to particulate suspensions for the use in superior laryngeal nerve blocks in Otolaryngology.
Our results have shown that both particulate (PS) and soluble (SS) steroid SLN block significantly improved post-treatment CSI in our cohort. When the improvement of CSI score was compared between the two groups a t-test has shown that it is not statistically significant ($p = 0.352$). However, our non-inferiority study made it evident that non-particulate steroids used in Superior Laryngeal Nerve (SLN) blocks prove to be just as effective as their particulate counterparts in reducing the severity of chronic cough. This discovery aligns with recent research in anesthesiology, where similar non-particulate steroid treatments have demonstrated extended regional block duration and effectiveness in managing chronic pain through the administration of steroids in the spine.\textsuperscript{74–76}

An intriguing aspect revealed in our study is the bimodal response distribution observed in both treatment groups, as depicted in Figure 3B. This suggests a fascinating nuance in how patients with refractory cough (RC) experience varying degrees of improvement in cough severity. The multifactorial nature of RC, compounded by the lack of definitive tests to pinpoint its neurogenic origin, intuitively explains this variability among patients.

While our review of the literature did not uncover any reported cases of embolization in SLN blocks, it is crucial to acknowledge the established risks highlighted in anesthesiology literature. Despite the absence of documented cases of embolization after SLN block, the recent adoption of this technique by laryngologists prompts us to advocate for further exploration of soluble steroids as a potentially safer alternative. The imperative here is to pave the way for more research that delves deeper into the safety aspects of soluble steroids, considering the established risks associated with particulate steroids.
Limitations

It is essential to recognize the limitations within our study. The relatively small cohort size restricted our ability to perform a thorough multivariable analysis, emphasizing the need for larger studies to confirm and expand upon our findings. Additionally, the variation in follow-up times, owing to the recent integration of dexamethasone in SLN blocks at our institution, limits our ability to make direct comparisons regarding long-term efficacy between the different steroid types. The retrospective nature of our study further adds a layer of limitation, emphasizing the necessity for prospective research with randomization and scheduled follow-up visits.

By disseminating these findings as a non-inferiority study, our intention is to lay the groundwork for future research that delves into the comparison of steroids in SLN blocks. The acknowledged limitations underscore the importance of conducting such research prospectively, employing randomization, and incorporating periodic follow-up visits to enhance the robustness of the results and their applicability to clinical practice.

Dissemination of Findings

Academic Conferences

The results of this research were presented at the 2022 Fall Voice Conference held in San Francisco, CA, USA, from October 6 to 8. The conference served as a platform to share our key findings with fellow professionals, researchers, and practitioners in the field of otolaryngology.
and rhinology. The presentation facilitated discussions, feedback, and potential collaborations with experts in the domain.

**Manuscript Submission**

A comprehensive manuscript detailing the outcomes of this study has been prepared and submitted to the "Annals of Otolaryngology and Rhinology" journal. As of the current status, the manuscript is under review. The decision to submit the work to this reputable journal aligns with the aim of contributing to the scholarly literature in the field. If accepted, the manuscript will be published, ensuring the broader dissemination of our research to the academic community.

**Conclusion:**

In conclusion, this retrospective cohort study's comprehensive analysis yielded compelling evidence indicating that SLN block utilizing soluble steroid dexamethasone is comparably effective to particulate steroids in mitigating the severity of symptoms in individuals with refractory cough (RC). Notably, this revelation, coupled with the acknowledged albeit low potential for particulate steroid embolization, presents a strong case for the widespread adoption of soluble steroids, specifically dexamethasone, as the primary choice for corticosteroid administration during SLN block procedures. However, it is imperative to acknowledge the limitations inherent in this study, notably the constraints related to sample size and significant variations in follow-up periods among participants. To address these constraints and further solidify the findings, future investigations should employ prospective study designs aimed at
meticulously comparing the efficacy and safety profiles of various steroids utilized in SLN blocks. Such prospective studies hold the promise of providing more robust and definitive insights into the optimal steroid choice for SLN block interventions in managing refractory cough, thereby enhancing clinical decision-making and patient care strategies.
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