Serial Intralesional Steroid Injection for Subglottic Stenosis: Systemic Side Effects and Impact on Surgery-Free Interval

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Abstract

Objectives. In-office serial intralesional steroid injections (SILSIs) have become a commonly used treatment for subglottic stenosis. We characterized the impact of SILSIs on the time between operating room visits and incidence of glucocorticoid systemic side effects.

Study Design. Retrospective case series.

Setting. Academic tertiary care center.

Methods. All patients with subglottic stenosis receiving SILSIs at 1 institution from 2016 to 2020 were included. Surgery-free interval was compared using paired t tests. Side effect incidence was calculated with Kaplan-Meier methodology for visualization.

Results. Nineteen patients and 207 procedures were included. The majority of patients were White (95%) and female (95%) and had idiopathic subglottic stenosis (53%). Mean surgery-free interval for all patients was 8.7 months (95% CI, 5.6-11.8) before initiating SILSIs. Of 11 patients with calculable surgery-free interval, 10 experienced improvement, with a mean surgery-free interval increase of 4.6 months (95% CI, 2.4-6.7). Seven patients have not required surgery since initiation of SILSIs, with a mean follow-up time of 28 months (95% CI, 25-31). Noncutaneous systemic side effects occurred at a mean 3.2 months (95% CI, 2.4-4.0) from first injection and included Cushing’s syndrome, increased intraocular pressure, central serous chorioretinopathy, and new insulin requirement in the setting of diabetes.

Conclusions. Ninety-one percent of patients who initiated SILSIs and had a subsequent return to the operating room experienced a mean 4.6-month increase in surgery-free interval. Systemic side effects of glucocorticoids occurred in 32% of patients after initiating SILSIs. This should be considered in preprocedure counseling and side effect monitoring during treatment.

Keywords

subglottic stenosis, serial intralesional steroid injections, side effects, Cushing’s syndrome, surgery-free interval

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Subglottic stenosis (SGS) is a narrowing of the extrathoracic airway at the cricoid cartilage and cricotracheal junction. SGS is often associated with intraluminal inflammation and submucosal fibrosis, particularly when occurring in the setting of autoimmune disorders such as granulomatosis with polyangiitis or idiopathic SGS.¹ There is no established standard treatment protocol for management of SGS.²,³ Multiple treatment options are commonly offered, such as open cricotracheal resection, endoscopic laser resection with adjunct medical therapy, laser or cold knife incision, airway dilation, intralesional steroid injection, and mitomycin application.⁴-⁶ Open resection offers more durable outcomes but a higher complication rate, whereas endoscopic treatments have lower risk of complications but typically require return to the operating room (OR) for symptomatic restenosis.⁷-¹⁰ Many patients opt for lower-risk endoscopic approaches over open surgical treatment, despite likely need for serial OR procedures.¹¹

In-office serial intralesional steroid injections (SILSIs) provide an option to stabilize airway patency, delay symptoms, and extend time between OR procedures. Small retrospective studies have shown up to an 8- to 12-month increase in surgery-free interval (SFI).²,¹²,¹³ This coincides with stable or even improved airway patency with SILSIs.¹⁴,¹⁵ Patients indicate less dyspnea, decreased vocal handicap, and improved...
voiced-related quality of life.\textsuperscript{16} While SILSIs have been rapidly and widely adopted within the SGS community, reports of outcomes remain limited to case series, and the clinical potential for corticosteroid side effects has only recently been described in the literature, such as transient hypothalamic-pituitary-adrenal (HPA) axis suppression and Cushing’s syndrome.\textsuperscript{17,18} Mild self-limited side-effect symptoms were also noted by 55\% of patients who were surveyed following SILSI administration.\textsuperscript{19} Adequate patient counseling requires understanding of the benefits and risks.

Aims of the current study are to evaluate for significant side effects following subglottic corticosteroid injection and to quantify the change in SFI between OR procedures in a cohort of patients with SGS treated with in-office steroid injections.

**Methods**

**Patient Population**

Patients treated at the University of Michigan from January 1996 to March 2020 with SGS were reviewed. Patient records were retrieved from the electronic medical record through ICD-9 and ICD-10 codes for laryngeal stenosis and tracheostomy complications (\textit{International Classification of Diseases, Ninth and Tenth Revision}; J95.5, J95.0, J38.6, J39.8, 478.74, 997.32, 519.19, 519.1, 519.02) and CPT codes used at our institution for laryngotracheal reconstruction and dilation (\textit{Current Procedural Terminology}; 31541, 31526, 31571, 31592, 31599, 31599.3, 31588, 31780).\textsuperscript{20} Patients were included if they were diagnosed with SGS and received in-office corticosteroid injections after surgical treatment, which we began performing in 2016. The historical treatment record prior to 2016 was included, if existing, to establish baseline SFI prior to initiation of SILSIs.

**In-Office Injection Procedure**

Injections were administered in clinic under flexible nasolaryngoscopic visualization with 4\% lidocaine gargle to anesthetize the larynx and trachea. Steroid was injected into the stenosis percutaneously or via sclerotherapy needle passed through the flexible endoscope channel. Triamcinolone (40 mg/mL) or betamethasone (6 mg/mL) was used per surgeon preference. Total steroid dose was decided by the surgeon at the time of injection and dependent on degree of stenosis and tissue visualization and access. Three injections were generally planned every 4 to 8 weeks following an endoscopic dilation. The injection schedule was often adjusted to consider multiple factors, primarily how rapidly the patient’s stenosis had recurred previously and patient travel logistics. Symptom severity, voice-related quality of life metrics, and degree of stenosis were factors considered in deciding when to administer additional SILSIs or return to the OR for an endoscopic procedure.

**Exposures and Outcomes**

Demographic data, relevant comorbidities, and SGS etiology were collected for each patient. All institutional treatments were recorded, such as cricotracheal resection, laser/cold knife incision, intraoperative steroid or mitomycin C, and SILSIs. Records from each steroid injection included medication used, dose volume, and dose concentration. Progress notes from every encounter in our health system after initiating SILSIs were reviewed to identify side effects and date of incidence. Betamethasone dose was standardized to triamcinolone equivalent for analysis. Primary outcomes were incidence of side effects and time between OR visits.

**Statistical Analysis**

Side effects were analyzed for type, frequency, and mean time of onset after steroid injection. SFI for individual patients before and after SILSIs was compared with $t$ tests, with means adjusted for clustering by patient. Data were collected and managed in REDCap (Research Electronic Data Capture) hosted at the University of Michigan.\textsuperscript{21,22} Data analysis was performed in Stata version 15.1 (StataCorp LLC). This study was approved by the Institutional Review Board of the University of Michigan (HUM00150934).

**Results**

**Study Population**

Nineteen patients were included in this study. A majority of patients were White (95\%) and female (95\%) with a mean age of 45 years (95\% CI, 42-45). One patient was Hispanic (5\%) and 1 was male (5\%). Idiopathic (n = 10, 53\%) was the most common SGS etiology, followed by iatrogenic (n = 5, 26\%), granulomatosis with polyangiitis (n = 3, 16\%), and relapsing polychondritis (n = 1, 5\%). Study demographics are shown in Table 1.

**Treatment Characteristics and Outcomes**

A total of 207 procedures were included, with 125 in-office intralesional steroid injections and 82 endoscopic procedures in the OR. Treatments were performed with triamcinolone (40 mg/mL) 97 times and betamethasone (6 mg/mL) 28 times. Triamcinolone dosage varied from 20 to 200 mg and betamethasone from 3 to 18 mg. Patients received between 1 and

### Table 1. Study Population Characteristics

|                | No. | %  |
|----------------|-----|----|
| Sex            |     |    |
| Female         | 18  | 95 |
| Male           | 1   | 5  |
| Race           |     |    |
| Hispanic       | 1   | 5  |
| White          | 18  | 95 |
| Diagnosis: SGS type | | |
| Granulomatosis with polyangiitis | 3 | 16 |
| Intubation     | 5   | 26 |
| Idiopathic     | 10  | 53 |
| Relapsing polychondritis | 1 | 5 |

Abbreviation: SGS, subglottic stenosis.
15 injections, with a median of 7 injections. Mean interval between injections was 2.7 months (95% CI, 2.1-3.4).

Mean follow-up time, defined as time from first to last visit in clinic, was 49 months (95% CI, 36-62). Mean follow-up time after initiating SILSIs was 24 months (95% CI, 22-27). Mean SFI for the entire cohort before initiating SILSIs was 8.7 months (95% CI, 5.6-11.8). Among 11 patients with multiple OR procedures before and after initiating SILSIs, 10 patients experienced improvement in SFI. In these 10 patients, mean SFI increased by 4.6 months (95% CI, 2.4-6.7): from 6.1 months (95% CI, 3.2-9.0) before initiating SILSIs to 10.7 months (95% CI, 6.6-14.8) after initiating SILSIs. For the 7 patients who have not returned to the OR since initiating SILSIs, mean follow-up time since first injection is 28 months (95% CI, 25-31) based on the most recent follow-up visit as an endpoint. SFI values for each patient are shown in Table 2.

Figure 1. Mean surgery-free interval of patients who returned to the operating room after initiating SILSIs. SILSI, serial intralesional steroid injection.
requirement in the setting of diabetes, rash, and new facial acne. Cutaneous side effects occurred in 2 patients on postprocedure day 0, while the other side effects occurred in 4 patients at a mean 3.2 months (95% CI, 2.4-4.0) from first injection (Table 3, Figure 2). Mean cumulative steroid dose in triamcinolone equivalents was 148 mg (95% CI, 64-231) before onset of symptoms. Comparatively, patients who had no side effects had a mean total dose of 581 mg (95% CI, 180-982). Time between injections in patients with side effects was 2.8 months (95% CI, 1.9-3.6) as compared with 2.7 months (95% CI, 1.8-3.6) in patients without side effects. Treatment courses in each patient with side effects are illustrated in a timeline plot in Figure 3.

### Side Effect Cases

#### Cutaneous Side Effects

Patients 6 and 12 developed rashes on the same day following their first steroid injection and have consistently experienced similar rashes with subsequent injections. Patient 6 experienced facial flushing and acne, while patient 12 had an urticarial-like rash on her arms, legs, and chest. Rashes in both patients have been mitigated with oral diphenhydramine taken on the same day prior to the procedure.

**Metabolic Side Effects**. Patient 3 is a 29-year-old woman with iatrogenic SGS who received a 4.8-month benefit to mean SFI after SILSI initiation, from 2.1 months pre-SILSI to 6.9 months post-SILSI. She presented to her primary care provider 4.6 months after initiating SILSIs with 53-lb weight gain, moon facies, and poor glycemic control and was diagnosed with Cushing’s syndrome. Because she was a high-risk surgical patient, the decision was made to continue SILSIs with reduced frequency.

Patient 9 is a 45-year-old woman with idiopathic SGS and well-controlled type 2 diabetes who noted significant hyperglycemia and developed a yeast infection 5 days after first injection of 200 mg of triamcinolone. She had similar glycemic control issues following subsequent steroid injections, which were managed by her endocrinologist with increased insulin glargine doses for 3 days starting the night before each injection. She ultimately had no increase in SFI after SILSI initiation; however, her initial post-SILSI dilation was prompted by the need to be intubated for unrelated surgery rather than symptoms requiring dilation.

**Ocular Side Effects**. Patient 2 is a 39-year-old man with iatrogenic SGS who received a 4.4-month benefit to mean SFI after SILSI initiation, from 2.0 months pre-SILSIs to 6.4 months post-SILSIs. He presented to ophthalmology for progressive vision changes 3.9 months after initiating SILSIs and was diagnosed with central serous chorioretinopathy. SILSI discontinuation was recommended by his ophthalmologist, and the patient has received only endoscopic dilation since.

Patient 13 is a 63-year-old woman with iatrogenic SGS who had only 1 endoscopic dilation before initiating SILSIs and has not yet returned to OR after SILSIs. Her
ophthalmologist noted increased IOP following her fourth injection, 126 days after initiation of SILSIs. Steroid injections were discontinued. One year later she had mildly symptomatic restenosis and underwent a single in-office steroid injection. She has had no recurrence of stenosis at last follow-up.

**Discussion**

In this case series of 19 patients with SGS with 125 intraleisional steroid injections, SILSIs improved the SFI by a mean 4.6 months when compared with endoscopic surgery alone in the same cohort prior to initiating SILSIs. In addition to 2 cutaneous side effects on the first day of administration, 4 patients in our cohort indicated systemic side effects that occurred at a mean 3.2 months after their first injection. These findings add to previously published literature on SILSIs for treatment of SGS, supporting the benefits of SILSIs while demonstrating significant risks. The study population matches the White female predominance of prior research in this space and represents multiple SGS etiologies. Length of time between injections and dose volume were similar to other published reports; however, use of betamethasone was unique to this study. Betamethasone is preferred by some surgeons because the solution does not obscure visualization in the event of extravasation from the injection site, as compared with opaque triamcinolone suspension. It was also used as an alternative steroid in some cases in an attempt to mitigate side effects. Betamethasone use did not appear to have an impact on clinical benefit or side effects.

**Figure 3.** Side effect timeline plots. Asterisks, first side effect; arrows, recurrent side effects. IOP, intraocular pressure; OR, operating room; SILSI, serial intralesional steroid injection.
Similar to Bertelesen et al12 and Pan and Rosow,13 we found an increased SFI with SILSIs, supporting this technique as a valuable therapeutic option. Our mean 4.6-month benefit to SFI was less than their observed effect but within the confidence interval. It is important to note that SFI benefit is underestimated in our study because 7 of the best-responding patients have not required return to the OR, with a mean post-SILSI follow-up of 3 times that of SFI in patients who returned to the OR. Longer follow-up would increase the mean SFI benefit in this cohort, while a larger sample size could allow for comparison of factors that may determine response, such as etiology, systemic disease burden, or number of previous procedures.

This study revealed a 32% incidence of systemic side effects in the medical record after SILSIs. While there are several reports in the literature describing outcomes with SILSIs, extant literature is lacking regarding clinically identified systemic side effects.12-19 Hoffman et al noted a similar rate of adverse effects (31%) but a different set of side effects incident to the injection procedure itself, including transient airway restriction, cough, nasal pain, and a single instance of possible hypercortisolism (weight gain, headaches, insomnia, restlessness).16 Multiple patients in the present study indicated discomfort with injection or a vasovagal response, but these were not included in our analysis.

A recent case report described Cushing’s syndrome in a patient with obesity and type 1 diabetes after receiving SILSIs for 10 months at a rate of 72 mg of triamcinolone per month.18 One patient in our cohort developed Cushing’s syndrome in half that time, with a significantly lower cumulative dose and greater time between injections. Studies of keloid treatment with triamcinolone injections have shown safe intradermal administration of up to 120 mg per month.23,24 Instances of iatrogenic Cushing’s syndrome are rare from keloid treatment and occur mostly in pediatric populations, but local and systemic side effects of injection occur in up to 63% of patients.25 The higher side effect rate in our study does not appear to be due to larger cumulative doses in a short period. The average interval between steroid injections was similar in patients who did and did not experience side effects, and mean cumulative steroid dose was actually less in patients experiencing side effects as compared with those who did not. This is consistent with a 6-patient pilot study that showed normalization of cortisol and the HPA axis within 7 days of 40 to 200 mg of SILSIs for SGS.17 Similarity in timing and dosage between patients with and without side effects supports the influence of multifactorial determinants of HPA axis sensitivity, such as sex, age, genetics, lifetime or current stress exposure, systemic inflammation, and body mass index.26,27

Other similar studies demonstrated that steroid injections affect blood glucose levels more in intra-articular knee injections than upper extremities, but the dose and the number of injections had no effect.28,29 Increased IOP is seen in triamcinolone intra-articular knee injection and oral steroid treatment, at a rate of 25% to 29%.30 One patient in our cohort experienced increased IOP and was receiving simultaneous knee injections of an unknown dose, which may have been the primary etiology or at least a contributor to her total systemic dosage. Central serous chorioretinopathy may also be caused by intra-articular, inhaled, and epidural steroid administration.31

Because there are no simple predictive factors for the incidence of corticosteroid injection side effects, patient counseling and close monitoring are important to quickly recognize side effects and appropriately adjust therapy.32 All 6 new side effects occurred within the first 5 months after SILSI initiation, indicating that the first several months may be most critical for monitoring. Specific screening questions, such as those by Celebi et al, have identified subtle side effects from SILSIs affecting mood, sleep, blood pressure, and menstruation and should be incorporated into each SILSI visit.19 We suggest that questions regarding weight gain, Cushingoid facial swelling, rash, glycemic control if applicable, and vision changes be included when screening patients for side effects. Patients should also be counseled on possible side effects prior to initiation of SILSIs and instructed to inform the surgeon immediately if these occur. In our cohort, ocular complications were diagnosed by ophthalmologists, while impaired glycemic control was recognized by the patients and their primary care providers. Patient-physician and interprofessional communication is necessary when side effects are not identified by the administering otolaryngologist. Mild and transient side effects, such as rash and impaired glycemic control, should not disqualify the patient from SILSIs as long as these effects are recognized and managed.

Variation in patient response and side effects may require deviation from our common protocol of 3 steroid injections every 4 to 8 weeks. In our cohort, injection intervals were increased to mitigate Cushing’s syndrome and discontinued for patients with ophthalmologic complications. Patients with transient side effects, such as rash or impaired glycemic control, were able to medically manage their side effects and maintain regular intervals. In an example of protocol deviation because of good SILSI response, patient 18 experienced a significant SFI extension since initiating SILSIs and has not yet returned to the OR. Instead of a fixed number, the patient received 15 injections spaced 8 weeks apart, which has doubled the SFI. A standardized regimen would allow better data collection and characterization of SILSI benefit but should be flexible based on individual patient response and discussion of risks and benefits between the patient and surgeon.

Conclusions from the study are limited by its small size, retrospective analysis, and variability in management and side effect screening. A larger percentage of patients with side effects may have been identified if standardized screening surveys had been administered to all patients undergoing SILSIs, as this may have identified symptoms that patients otherwise did not report to their physicians. The ocular complications cited in this study are known to be associated with steroids, although it is impossible to determine whether SILSIs were the direct cause of these conditions in these patients. We included patients with different etiologies of SGS, as well as variable treatment doses and schedules, limiting the ability to determine the effects of SILSIs on SFI.
While the small sample size prevented subgroup analysis by etiology of stenosis, we acknowledge that idiopathic, autoimmune, and iatrogenic SGSs are different disease processes, and further study is needed to determine the effects of SILSIs across these diagnoses.

This case study contributes to growing evidence of an association between SILSIs and the systemic side effects of glucocorticoids, specifically ocular complications and Cushings syndrome, which is an important consideration in counseling about risks of this treatment approach. Further work is necessary to better define the incidence and severity of these side effects in a prospective manner among a larger patient cohort.

Conclusion

This study adds to current literature supporting the benefit of SILSIs for prolonging SFI and demonstrates a significant incidence of systemic side effects associated with corticosteroids. These data inform counseling of patients with SGS who are considering this treatment. Prospective studies investigating the use of SILSIs for SGS should include specific monitoring for and documentation of corticosteroid-related adverse effects.

Author Contributions

Andrew J. Neevel, design, data collection, analysis, presentation; Ari D. Schuman, design, data collection, analysis, presentation; Robert J. Morrison, data collection, presentation, review; Norman D. Hogikyan, data collection, presentation, review; Robbi A. Kuper, design, data collection, presentation, review

Disclosures

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