Urticaria and Angioedema after Intraturbinal Injection of Steroids

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Abstract

Intraturbinal corticosteroid injections have been used for over sixty years. Their use has significantly decreased since the late 1970’s when reports of blindness following corticosteroid injections were made. The largest case review regarding complications was last published in 1982 and reported a risk of blindness of 0.006%.

The purpose of this study is to report on 3 patients that developed either urticaria or angioedema after intraturbinal injections of steroids, complications not yet reported after this route of administration. Risk for complication development, administration technique and precautions are also discussed.

Key Words: intraturbinal steroid injections, urticaria, angioedema, allergic rhinitis, nasal obstruction, chronic sinusitis, sinus headache.

Introduction

Intraturbinal corticosteroid injections are useful for the control of symptoms that directly or indirectly are related to nasal allergies. Management of nasal allergies relies on allergen avoidance, medications and immunotherapy. When medical treatment fails or when there is a symptom-breakthrough during immunotherapy administration it is sometimes necessary to administer steroids as these patients are usually very symptomatic. In our office these patients are candidates –in the short term- for intraturbinal corticosteroid injections.
Intratobular corticosteroid injections have been in use for at least the last sixty years. Despite the first published description dating back to 1951, these injections are not widely used probably for the perceived risk for potential visual disturbances after their administration. The reported potential complications for this procedure include minor bleeding, facial flushing (reported to occur in 1-2% of the cases), lumbar pain, vision problems (transitory or permanent) and vasovagal reactions.

**Bleeding:** As the turbinates are very vascular and because when an intratobular injection is given the nasal mucosa is usually inflamed, it is only logical to expect some minor bleeding after the injection. Still some patients reported this as a complication.

**Facial flushing:** Diffuse erythema that develops soon after the injections and involves the cheeks bilaterally. It is not a frequent occurrence and has also been observed after intra-articular steroid injections. Because it has also been observed after water soluble steroid injections it is not thought to be related to the repository crystals but to the steroid itself. It resolves in 24-48 hours without any need for medical intervention.

**Lumbar pain:** Occurs very rarely and usually subsides in less than 30 minutes. It can also be observed after an IM steroid injection and it is thought to be an allergy to the vehicle.

**Vaso-vagal reactions:** Near syncope events than can potentially occur in some patients any time that needles are used. ("Needle reaction" or "needle phobia").

**Blindness:** The major catastrophic and feared complication. In 1962 there was a report of a case of blindness after an intratobular corticosteroid injection and several other cases were reported in the 1960’s and 1970’s. Combined with the introduction of intranasal steroids in the 1980’s these reports probably explain the marked decline in the use of intratobular corticosteroid injections by the otolaryngologist. Blindness can also occur after injections of steroids in other areas of the head and neck including scalp, oral cavity or facial skin. Blindness after corticosteroid injections has also been reported for other areas of the body even though the proposed mechanism for the development of blindness is different. Nevertheless there are authors that have used intratobular corticosteroid injections extensively and for a long period of time with satisfactory results:

Mabry administered more than 13,000 injections during a period of 25 years without any case of visual loss. Kabaker administered 36,000 injections without any case of blindness. Dutton reported using the procedure more than 4,000 times by himself and 10,000 times in his practice, and cited collective administration of more than 100,000 injections without complications. Mc Cleve et al reported 60,000 injections with 2
cases of transient visual loss and Becker reported on 189 patients who underwent bilateral intrapolyg steroid injections without any cases of visual disturbances. Mabry had information on 19 cases of visual disturbances related to intraturbinal corticosteroid injections and reported on 10 of those. Even though he never encountered such a complication, through an analysis of published literature, he calculated the risk of temporary or permanent visual disturbance as 0.006%. The suggested mechanism for visual disturbances is thought to be related to the presence of direct intravascular injection with retrograde flow of agglomerated particles of injected material into the ophthalmic artery and anterograde embolization into its branches with reflex vasospasm as there are anastomoses between the nasal and the ocular circulations. The anterior and posterior ethmoidal arteries are derived from the ophthalmic artery, its two terminal branches are the frontal and dorsal nasal arteries and branches of the sphenopalatine artery anastomose with the ophthalmic artery. For cases of blindness after scalp injections the suggested mechanism is thought to be related to embolization though anastomoses between superficial temporal artery and ophthalmic artery circulations.

The concept of retrograde embolization in an arterial system implies forceful injection to overcome arterial pressure. Other factors mentioned as important in the development of blindness are the total injected volume and the size of the injected particles. Because sedimentation and agglomeration can occur when the injectable suspension is allowed to stand, shaking prior to injection, and using the products with the smaller particles, like Triamcinolone, is advisable (even though there are cases of blindness reported after the injection of Triamcinolone). Amaurosis was also reported after injections of local anesthetics and nerve blocks in dental, oral, nasal and orbital procedures. The mixture of steroids with Epinephrine is not advised.

The purpose of this study is to report complications that developed in 3 patients after intraturbinal corticosteroid injections in a private office over a 7 year 3 months period, to analyze the calculated risk of such complications and to review technical aspects of the procedure.

Methods

A retrospective chart review was done, looking for patients who received intraturbinal corticosteroid injections under the supervision of the Principal Investigator (DS) in his private office. IRB approval was obtained through the
Institutional Review Board of Trinitas Regional Medical Center of Elizabeth, New Jersey.

The search was performed by cross referencing the CPT code for Intraturbinal Injections (Injection into turbinate(s), therapeutic: 30200) and the ICD-9 diagnostic codes for allergic rhinitis (477.9), chronic sinusitis (473.9), nasal polyps (471.9), turbinate hypertrophy (478.9) sinus headaches (784.0) and nasal obstruction (478.19) in adults over the age of 18 treated from 1/1/05 to 3/31/12. Medical records of these identified patients were then reviewed to identify any complications associated with these injections.

Triamcinolone acetonide injectable suspension USP (Kenalog-40. Bristol-Meyers Squibb Co, Princeton, NJ) was used in all cases. This product is only FDA approved for intramuscular and intra-articular use however it is used in an off-label manner for intraturbinal and intradermal injections by otolaryngologists, plastic surgeons and dermatologists.

Injection technique (Table 1).
With the patient positioned in a 45 degree decubitus position, the anterior nose is packed with pledgets wet with an anesthetic/decongestant mixture. (We use 1% Lidocaine with Epinephrine 1/100,000). The Kenalog vial is thoroughly shaken and then, with a 1.0 cc allergy syringe (Terumo catalog # SS10A2713IDT: 27Gx1/2”) the suspension for injection is drawn into the syringe and pushed back into the vial 3 times until finally drawing the suspension in the fourth draw. Volume loaded is 0.50 mL of Kenalog 40, for a total dose of 20 mg that will be administered half in each turbinate. At this time the cotton pledgets are removed. The anterior tip of the inferior turbinate is exposed with a nasal speculum and the suspension is slowly injected in the sub mucosa of the tip of each inferior turbinate. A total of 0.25 mL is injected into each turbinate (or 10 mg per side). The needle is introduced “parallel” to the mucosal surface trying to introduce only the bevel of the needle so that the injection is very superficial, immediately under the mucosa. The injection is given slowly and gently avoiding any pressure during injection and attempting to raise a mucosal wheal with the injected material producing a superficial blanching similar to the one attained by injection of the septal mucosa prior to a septoplasty. After the injection, dry cotton nasal pledgets are placed to control any superficial bleeding at the site of injection and patients are maintained in the reclined position for a few minutes. Upon removing the dry pledgets patients are warned that if they blow their noses it is likely they will observe bloody mucous that will resolve quickly. By keeping the patients in a semi-horizontal position during and after the procedure vaso-vagal reactions almost never develop.
**Indications for injections**

Patients older than 18 years of age with one or more of the following clinical presentations:

1) Severe nasal allergies that are not responding to usual medication. (A frequent presentation in our office is the patient with severe allergic conjunctivitis).
2) Severe nasal obstruction due to allergies or as a complication of the continued use of topical decongestants (Rhinitis Medicamentosa).
3) Severe sinus pressure or pain in a patient with chronic sinusitis (with or without nasal obstruction).
4) Large nasal polyps when patient complains of severe nasal obstruction and/or sinus pain. (In this case the injections are given not only in the turbinates but also in the polyps themselves).

These injections are not administered when patients report an “allergy to cortisone” or in cases of acute sinusitis, while patient is having fever or mucopurulent nasal discharge, (even though common cold has been reported as one of the indications) but they are administered when there is a resolution of the acute phase if patient remains with sinus pain and/or nasal obstruction or persistent nasal or post nasal discharge.

**Results**

Chart review yielded 2,230 patients that received bilateral intraturbinal corticosteroid injections (for a total of 4,460 injections). It can be calculated (as a simple average) that 51 injections were given per month or 615 per year.

In 3 cases (described below) the patients developed an immediate allergic reaction requiring medical intervention (Table 2). In all cases the reaction involved the facial skin (Urticaria in 2 cases and Angioedema in 1 case), and only 1 case had minor oropharyngeal symptoms. There were no cases of transitory or permanent visual loss. There were no other major complications.

While these complications have been reported with parenteral corticosteroids in other areas of the body they have not yet been reported after intraturbinal injections.

In our hands, the risk of an allergic reaction to intraturbinal injection of Kenalog is 3 in 2,230 patients or 0.0013 % which is lower than the reported risk of blindness of
Calculating for the total number of injections the complication risk is 3 cases out of 4,460 injections or 0.00067%. There were no cases of transitory or permanent visual disturbances during this period of 7 year 3 months but the senior author has been using these injections for more than 20 years without ever encountering this type of complication.

Case reports:
Case 1: A 47 year old female with a past medical history significant for lupus and severe allergic rhinitis presented in January 2008 for complaints of severe nasal obstruction and bilateral facial sinus pain. She had been treated intermittently by her primary care doctor with Solu-Medrol (methylprednisolone sodium succinate) for her lupus and her seasonal allergy exacerbations. She underwent intraturbinal steroid injections (following above described technique). A few minutes after the injection the patient developed a few erythematous, itchy wheals of different sizes on her face and arms consistent with urticaria. She was in no apparent respiratory distress and there was no sensation of chest tightness, shortness of breath, or palpitations and patient did not have cough, hoarseness, stridor or facial flushing. Voice was normal, lungs were clear to auscultation. The patient was treated with Diphenhydramine 50 mg IM and Montelukast 10mg PO attaining a good response. She was monitored for approximately one hour and then released home. A follow-up phone call later that evening revealed complete resolution of her symptoms with improvement in her nasal obstruction.

Case 2: A 25 year old female with no significant medical problems presented in April 2008 for complaints of severe nasal obstruction and facial sinus pain. She was treated with intraturbinal steroid injections. Shortly after the injection patient developed diffuse facial erythema, a tickle in the throat, and need to clear her voice. She developed a swelling in the left eye-brow. She was in no apparent respiratory distress and there was no sensation of chest tightness, shortness of breath, or palpitations and patient did not have cough, hoarseness, stridor or facial flushing. Voice was normal, lungs were clear to auscultation. Patient was promptly treated with 0.3 mg of Epinephrine IM and Benadryl 50 mg IM which completely resolved her symptoms. She was monitored for another hour and then discharged. A follow-up phone call later that evening revealed complete resolution of her symptoms with improvement in her nasal obstruction.

Case 3: A 46 year old female with no significant past medical history presented with multiple allergy symptoms including nasal obstruction and severe sinus pressure. She
was treated in March 2012 with intraturbinal injections of Kenalog and within a few minutes she developed 2 pruritic wheals on the right side of the face. She was in no apparent respiratory distress and there was no sensation of chest tightness, shortness of breath, or palpitations and patient did not have cough, hoarseness, stridor or facial flushing. Voice was normal, lungs were clear to auscultation. Patient was treated with oral medications (Cetirizine 10 mg PO and Montelukast 10 mg PO) and responded well. She was monitored in the office for 1 hour and then discharged. A follow-up phone call later that evening revealed complete resolution of her hives and her allergy symptoms were also under control.

**Discussion**

Patients with allergic rhinitis often develop nasal obstruction that can be severe enough to adversely affect patient’s quality of life. Nasal obstruction is one of the most common complaints and the most severe symptom affecting the allergic patient mainly when having perennial symptoms. Beyond the patient with nasal allergies, other patients that become candidates for these injections, when failing to respond to medical management, include:

a) The pregnant patient in the third trimester that may develop severe nasal obstruction which could significantly affect her quality of life.

b) Patients with chronic sinusitis who can develop severe headaches and sinus pressure, sometimes unresponsive to topical intranasal steroids or allergy medications.

c) Patient with rhinitis medicamentosa with their characteristic nasal obstruction that is sometimes severe and difficult to manage. For these patients, intraturbinal steroid injections work extremely well providing prompt symptomatic relief in the majority of cases. In the experience of the senior author (DS), only a handful of patients over the years have required a course of oral steroids after failing to respond to a bilateral intraturbinal steroid injection.

d) Patients with nasal polyps, if treated with intraturbinal steroid injections and intrapolymp steroid injections, attain not only symptomatic relief but also reduction in polyp size. Becker et al. advocated intrapolymp steroid injections reporting a significantly lower rate of complications than with polyp surgical excision and suggested that steroid injections may decrease the need for further surgical removal of polyps.

Our experience, in agreement with published literature, shows that intraturbinal corticosteroid injections are well tolerated. While we never encountered any case of
visual disturbances, we believe that in order to avoid this complication it is very important to use a careful injection technique as described elsewhere\textsuperscript{4,14} and also detailed here (see “Injection technique” in Methods above and Table 1) paying particular attention to:

a) Application of a topical decongestant to decrease the chance for intravascular injection.

b) Using a suspension with small particles like Triamcinolone to decrease the chance of large particulate-aggregates.

c) Injecting very slowly avoiding any pressure during the injection to prevent pushing aggregated particles in a retrograde fashion. If the mechanism of embolization is a retrograde flow from the tip of the turbinate into the ophthalmic artery via the ethmoidal arteries, one should assume that a significant force needs to be applied over the injected suspension for the particles to go through anastomoses all the way back to the ophthalmic artery where anterograde embolization can then occur. Therefore it has to be assumed that it is extremely important to inject slowly and to avoid any pressure over the syringe embolus. Very infrequently, we encounter resistance when attempting to push the embolus (feeling as if the embolus is “stuck”). In these cases we withdraw the syringe, squirt a few drops of the suspension in the syringe so as to “wash” the needle (in case there was a particulate aggregate) and then re-inject in a different area of the anterior turbinate.

In support of the importance of proper technique is the fact that in 2 cases of transient visual loss reported by Mc Cleve et al the nasal mucosa had not been topically treated with an anesthetic-decongestant mixture.

While most of the authors use a 25 G x 1.5 inch needle, we use a 27 G x ½ inch needle. We feel that a smaller diameter will potentially make it more difficult for the material being injected to agglomerate and that a shorter needle will prevent accidental injection into the more posterior aspect of the inferior turbinate and therefore away from nasal blood vessels that anastomose with the retinal circulation. It is advised in the literature not to administer the injections in the nasal septum, middle turbinate or posterior aspect of the nose.\textsuperscript{11}

A case of transient visual loss after intraturbinal injection was reported in 2003.\textsuperscript{26} The injection technique in this case appears to be in accordance with the parameters suggested in the published literature so it is difficult to understand why the complication occurred. The author also describes a blanching with flushing of adjacent areas of that same side of the face. Is it possible that the vasospasm is an allergic reaction? Reactions to corticosteroids are known to occur and case reports have been published since the early 1950’s.\textsuperscript{19,27} Topical and parenteral medications
Urticaria and angioedema

have been implicated in cases of immediate and delayed reactions to multiple different corticosteroid molecules. These reactions can be true allergic reactions\(^\text{27, 28}\) even though in the majority of the cases the mechanism has not been proved.\(^\text{19, 27}\)

While there are case reports of reactions to the vehicle\(^\text{27, 28}\) the majority of the reactions are related to the corticosteroid itself.\(^\text{19, 27, 28}\) Because hydrocortisone is an endogenous hormone it is postulated that the added chemical chain to the basic molecule is responsible for eliciting the reaction and these reactions are quite specific (probably related to the hapten capabilities of the added molecules), for example a patient can react to the succinate form but not to the acetate form of the same drug.\(^\text{28}\)

There are no clear predisposing factors but in general it is observed that when a reaction occurred, a large amount or rapid administration (IV or IM) of the corticosteroid was given.\(^\text{19, 28}\)

There are case reports of severe reactions to corticosteroids that occurred in asthmatics with aspirin sensitivity\(^\text{19, 27}\) but the role of aspirin intolerance as a predisposing factor remains controversial.\(^\text{28}\)

The fact that steroids were previously tolerated does not preclude a future reaction and cases of systemic reactions to parenteral steroids occurred in people that tolerated oral administration.\(^\text{27}\)

The 3 cases herein reported pertain to female patients and all had skin involvement (2 cases Urticaria and 1 case Angioedema). One case only (case #2) had minor systemic symptoms. The patient in case #1 clearly stated she had uneventfully received Solu-Medrol (methylprednisolone sodium succinate) prior to this reaction, which is in agreement with the possibility of tolerating one corticosteroid but reacting to another one.\(^\text{27}\) It is possible that in the 3 cases presented here the patients reacted to the Triamcinolone itself and not to the excipient.\(^\text{19, 27, 28}\)

Unlike systemic steroids, the use of intranasal steroids sprays\(^\text{31}\) and intraturbinal steroid injections\(^\text{10, 29, 30, 32}\) have not been identified to have significant effect on the hypothalamic-pituitary-adrenal (HPA) axis. Intranasal steroid sprays, even though used very frequently, sometimes fail to provide symptomatic improvement and their use can be complicated by a perforation of the nasal septum.\(^\text{33, 34}\) Intraturbinal steroid injections have the efficacy of oral steroids, while lacking their side effect profile\(^\text{29}\) but there is no information on long term administration of intraturbinal injections. High doses of inhaled steroids were reported to elicit some HPA suppression\(^\text{35}\) and long term administration of intramuscular injections were reported to significantly affect the HPA axis.\(^\text{36}\) Based on the above facts we therefore think that frequent administration of intraturbinal corticosteroid injections should be avoided. In our office we do not administer more than 3 injections in a 1-year period.
Diabetic patients can also be treated with these injections. Even though diabetic patients are routinely warned that the blood sugar levels need to be monitored after the injections, we had only one instance of a patient that developed a decompensation of blood sugar levels after intraturbinal corticosteroids injections.

Intraturbinal steroid injections, with their limited side effect profile and prompt onset of action, usually extending over several weeks, are ideal in providing symptomatic relief in difficult-to-manage patients therefore they should be considered as a safe and cost effective treatment option but they should not replace definitive medical or surgical treatment of the underlying disease process. These injections provide a prompt response that usually lasts long enough to enable implementation of other treatment interventions.

This is a retrospective chart review and therefore has the inherent limitations of this type of study. While it is clear that except for the complications reported here there were no major complications, by the nature of the review, it is not possible to know if there were any other complaints not reported by the patients, neither is it possible to know how many developed the minor complications that occur on occasion like the facial flushing or lumbar pain.

There are questions that are not yet fully answered:

a) Are intraturbinal injections of corticosteroids more effective than intramuscular injections of corticosteroids?

There is some evidence that intraturbinal injections are more effective than intramuscular injections. In support of this assumption we can add anecdotal information: in our office we often see patients that recently received (and failed to respond to) an IM injection of steroids given by another physician. These same patients promptly respond to an intraturbinal injection given at the time of the visit at our office. Still there is no evidence supporting this fact based on the use of a validated instrument (like SNOT-20 or similar) used to evaluate symptoms before and after both types of injections.

b) Is an allergic reaction or complication to an intraturbinal injection of corticosteroids more likely than when an intramuscular injection is administered?

While over the years we have seen patients that describe real anaphylactic reactions to intramuscular injections of “cortisone” it is not possible at this time to know which route of administration is more allergenic or has more complications.
Future considerations would include a prospective study, with symptom scoring immediately before and after the injections, evaluation of minor and major complications and ideally having also a similar group of patients treated with intramuscular injections as this would provide information as to which route of administration provides better clinical results and if there is a difference in the rate and type of reactions that occurred in relation to the route of administration. Obviously this type of research is difficult to accomplish in a private practice setting, but it would be ideal to be done in a University setting.

Conclusions

1) Intraturbinal injections of corticosteroids are safe and extremely effective.
2) In our experience the risk of an allergic reaction to an intraturbinal injection of Kenalog is 0.0013% for the total number of patients (or 0.00067% for the total number of injections).
3) There have been no cases of blindness or other visual disturbances in this study.
4) Injections should be administered slowly, and syringe embolus should not be pushed if resistance is encountered.
5) The use of intraturbinal corticosteroid injections does not replace definitive medical or surgical treatment of the underlying disease process.
6) Intraturbinal corticosteroid injections should be considered a useful tool in a clinician’s armamentarium for the treatment of nasal obstruction and facial pain in patients with allergic rhinitis, chronic sinusitis (with or without nasal polyps), rhinitis medicamentosa and rhinitis of pregnancy.

References


12) The Bartleby.com edition of Gray’s Anatomy of the Human Body. The internal Carotid Artery. A.7 The Ophthalmic artery (Fig 514).


21) Between March 30 2012 and June 6 2012 the following databases were searched not finding any references of Urticaria or Angioedema after intraturbinal injection of steroids: PubMed, Medline, Cochrane and Ebsco Host.


Table 1: Safe Injection Technique for Intraturbinal Steroid Injection

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>Apply pledgets with anesthetic/decongestant mixture</td>
<td>Vasoconstriction prevents intravascular injection and retrograde flow</td>
</tr>
<tr>
<td>2)</td>
<td>Shake Vial; Load 0.50 mL of suspension through thin needle (27G).</td>
<td>Helps to disperse particles in suspension avoiding large conglomerates</td>
</tr>
<tr>
<td>3)</td>
<td>Draw and re-inject volume 3 times before finally drawing in the 4th draw</td>
<td>Helps to further disperse particles</td>
</tr>
<tr>
<td>4)</td>
<td>Inject slowly into anterior third of inferior turbinates under direct visualization, injecting superficially (blanching) into submucosa (0.25L/side or 10 mg in each turbinate).</td>
<td>Away from vascular spaces avoiding possibility of direct intravascular injection</td>
</tr>
<tr>
<td>5)</td>
<td>Avoid pressure while injecting</td>
<td>Decreases chance of retrograde embolization</td>
</tr>
<tr>
<td>6)</td>
<td>Apply dry pledget</td>
<td>Controls mild bleeding always encountered upon injecting the nasal mucosa</td>
</tr>
<tr>
<td>7)</td>
<td>During and after injection keep patient in a semi-reclining position</td>
<td>Decreases risk of vaso-vagal reaction</td>
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Table 2. Complications

<table>
<thead>
<tr>
<th></th>
<th>Case #1</th>
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<tr>
<td>Urticaria</td>
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<td>Throat tickle</td>
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<td>Visual problems</td>
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<tr>
<td>Treatment</td>
<td>D IM, M</td>
<td>E, D IM</td>
<td>C, M</td>
</tr>
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</table>

Resp: Respiratory

SOB: Shortness of Breath
D: Diphenhydramine
IM: Intramuscular
E: Epinephrine
C: Cetirizine
M: Montelukast

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