

Effect of Intraorbital Steroid Injections on Intraocular Pressure in Thyroid Eye Disease

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Abstract

Purpose: To study the effect of orbital steroid injections administered in the treatment of thyroid eye disease (TED) on intraocular pressure (IOP).

Methods: Retrospective chart review of consecutive patients over 70 months with active thyroid eye disease (TED) seen in a referral oculoplastic practice who underwent orbital steroid injections.

Results: The clinical records of 56 patients were included in the study. There were 51 females and 5 males; 43 (77%) were Caucasian; the average age was 50 years old. A mean number of 3.5 injections (range 1-12) were given per patient resulting in 91 encounters being examined. Injections consisted of dexamethasone in all cases with addition of betamethasone in 49 cases, methylprednisolone in 3 cases and triamcinolone in 3 cases. Pre-injection intraocular pressure (IOP) was recorded in 42 instances and post-injection IOP was recorded in 26 instances. The average time interval to next follow up was 9.4 weeks and the average time interval to next injection was 17.75 weeks. There was no increase in the mean pre-injection vs. post-injection IOP (short-term effect), nor in the first-recorded vs. last recorded IOP (long-term effect). In 73 instances, subjective response to injections with respect to swelling was recorded: in 46/73 (63%) cases swelling was noted to be reduced, in 19/73 no change was recorded and a worsening of swelling was reported in 8 cases. Diplopia improved in 13 cases and worsened in 4 (n=17).

Conclusions: No statistically significant rise in intraocular pressure was observed following orbital steroid injections.

Keywords: Thyroid ophthalmopathy; Thyroid eye disease; Graves' disease; Corticosteroid; Injections; Intraocular pressure

Introduction

Corticosteroids are the mainstay of treatment in active thyroid eye disease (TED). However, there is a risk of multiple systemic complications from oral and intravenous administration of steroids [1]. Intraorbital steroid injections are primarily used as an adjunct therapy during the active inflammatory phase of TED to decrease anterior orbital soft tissue swelling, and are occasionally used in treatment of extraocular muscle (EOM) restriction. The use of orbital steroid injections in the treatment of TED has a long history with the first case series reported in 1966 [2]. There is wide divergence amongst and even within various medical centers as to the use of periocular/orbital injections in the treatment of TED [3]: some clinicians never use this mode of therapy, whereas others use this routinely. There is also great variability with regard to the agents used (methylprednisolone, [2,4] triamcinolone [3,5-7]), indications, observed effects, and observed side effects. Some studies have reported reduction in lid retraction, strabismus, exophthalmos, [2,4,5-7] and even size of extraocular muscles on CT scans [5]. We currently use a mixture of dexamethasone (Dexamethasone Sodium Phosphate, Baxter, Deerfield, IL) and betamethasone (Celestone Soluspan Injectable Suspension, Schering-Plough, Kenilworth, NJ) to treat periorbital swelling in patients with active TED.

At present, triamcinolone appears to be the agent with the most published data. Some of the studies reported no complications [5] while others have noted several complications ranging from injection-related effects (retrobulbar hemorrhage) [4] to steroid-related effects. Steroid-related complications have included glaucoma, ranging from cases easily controlled with medications [2,3,6,7] to a single reported case requiring surgical intervention [6]. Also reported were two cases of cataract progression in elderly patients [7] and a case of transient hirsutism [6].

In our experience, patients have only experienced injection site ecchymosis, without glaucoma or cataract formation/progression; we have not observed an increase in IOP in the past. Therefore, we analyzed retrospective data at our practice to determine whether an increase in IOP could be detected in our series of patients.

Methods

After institutional review board approval was obtained, the office billing system was used to identify all patients within the study period from January 1, 2004 to October 30, 2009 who carried a diagnosis code of Thyroid Eye Disease (TED) 242.90 or 242.00, and had undergone a steroid injection (CPT 11900). All patients were seen by the senior author (MAS). The 56 patients' records were analyzed. Twenty five were excluded for the following reasons: chart not located, no injection given, injection given for reason other than TED, injection given outside study period. The remaining charts were reviewed.

The main study variables of IOP were compared in each eye in two ways: comparing preinjection to postinjection IOP, and comparing first visit IOP to last visit IOP. To analyze the repeated measurements of IOP pre and post injection, the geometric means of IOP pre and post injection were calculated, and linear regression models with generalized estimating equations (GEE) were used to account for within-subject correlation. To test the difference of IOP between first and final visit, paired t-test was used. Additionally, a change in exophthalmometry measurements was also compared using the same technique. All analyses were performed using SAS 9. 2 (SAS Institute, Cary, NC).

A mixture of dexamethasone and betamethasone with 0. 1 cc of 1% or 2% lidocaine with epinephrine was injected using a short 30-gauge needle. In anterior orbital injections, a 30-gauge short (1/2 inch) needle was placed in the lateral 1/3 of the eyelid, directed parallel to the orbital rim, to inject behind the orbital septum. In cases of restrictive strabismus during the active phase of TED we administered deeper injections, directing the needle posteriorly. In posterior injection, a 30-gauge short needle was placed through the lower lid, lateral to the inferior rectus, and directed posteriorly (“retrobulbar block”-like direction). These surgical techniques are well documented by other authors [3].

Of note, while not specifically approved for the treatment of TED, both dexamethasone and betamethasone solutions are FDA approved for the treatment of ocular inflammatory conditions [8,9]. Active TED can be included under that rubric.

Results

There were 56 patients included in the study. The majority of the study patients were women (91%), white (77%) and middle aged (average age 51; Tables 1 and 2). There were 170 injection cases: 100 (59%) were given for swelling and/or lid retraction, 19 (11%) were given for strabismus, in 9 (5%) cases an injection was administered in both the anterior and posterior fashion (swelling and strabismus) and in 42 (25%) cases the indication for injection was not clear from the chart.

Variables	Values	n (%)
Sex		
	Male	5 (8.93)
	Female	51 (91.07)
Race		
	Not recorded	3 (5.36)
	White	43 (76.79)
	Black	3 (5.36)
	Hispanic	6 (10.71)
	Asian	1 (1.79)

Table 1: Patient demographics

Many patients received multiple injections during their course of treatment. After excluding incomplete charts 91 encounters of 56 patients were examined (Table 1). Each patient had an average of 3.5 injections (Table 2). Injections consisted of dexamethasone in all cases

with addition of betamethasone in 49 cases, methylprednisolone in 3 cases and triamcinolone in 3 cases. Pre-injection intraocular pressure (IOP) was recorded in 42 instances and post-injection IOP was recorded in 26 instances (Table 3). The IOP did not rise in a statistically significant manner either following the injections or at the last follow up examination. In both cases the IOPs were lower: following the injections and at last examination ($p > 0.01$; Table 3).

Variables	N	Mean (Std)	Mean (Min, Max)
Age (in years)	56	50.80 (11.30)	50 (24, 78)
Average number of injections per patient	56	3.53 (2.72)	3 (1, 12)
Average duration of thyroid disease at first injection	29	2-4 years	2-4 years (0-6 months, 10+ years)
Average duration of ocular symptoms at first injection	40	6 months-1 year	6 months-1 year (0-1 months, 7-10 years)

Additional Variables: whether the patient was on glaucoma medication at the time of injection; location of injection; mixture of steroids used; presence of diplopia and lid retraction; status of orbital swelling documented on a subsequent visit; whether any additional TED surgery was performed; and whether the patient had undergone thyroidectomy or radioactive iodine treatment during the course of their systemic thyroid disease.

Table 2: Clinical Variables

IOP change with each injection				
	Pre Mean in mmHg (SE)	Post Mean in mmHg (SE)	Change Mean in mmHg (SE)	P value
IOP OD	15.41 (0.41)	14.97 (0.49)	-0.44 (0.29)	0.13
IOP OS	15.56 (0.45)	15.05 (0.49)	-0.51 (0.23)	0.022
IOP change from first visit to last visit				
	FirstMean in mmHg (SE)	LastMean in mmHg (SE)	Change Mean in mmHg (SE)	P value
IOP OD	15.25 (0.58)	15.00 (0.66)	-0.25 (0.89)	0.78
IOP OS	16.89 (0.75)	15.63 (0.61)	-1.26 (0.83)	0.15

Table 3: Changes in Intraocular Pressure (IOP)

Examining the data for secondary outcomes: change in swelling and diplopia (prior to excluding incomplete charts) produced the following results (Table 4). In 81 out of 170 cases response to injection was not recorded. In 73 instances, subjective response to injections with respect to swelling was recorded. In 46 of 73 cases (63%), swelling was noted to be reduced, no change was recorded in 19 (26%) encounters and a worsening of swelling was reported in 8 cases (11%).

Nineteen injections were given for EOM restriction. There were 18 total EOM’s targeted. In several instances a perimuscular injection was given at the time of an anterior (eyelid injection) and in several cases more than one muscle received a perimuscular injection. Formal muscle balance measurements were not taken at each follow up exam. Therefore, prism diopter changes were not recorded or analyzed. When patients were queried and response recorded, diplopia improved in 13 (76%) cases and worsened in 4 (24%) (n=17). There was no statistically significant change in exophthalmometry measurements following injections (Table 5).

Swelling Response	N=73
Improved	46 (63%)
Worse	8 (11%)
No response	19 (26%)
Diplopia Response	N=17
Improved	13 (76%)
Worse	4 (24%)
Not recorded: 81. No follow up: 4. Combination cases (both lid swelling and diplopia): 5. Diplopia improved in all 5 cases of combined injections, swelling improved in 4 and worsened in 1 of the 5. Total cases: 170	

Table 4: Subjective response to injections

Exophthalmometry measurements: change from pre- to post-injection visit				
	Pre-Injection Mean in mm (SE)	Post-Injection Mean in mm (SE)	Change Mean in mm (SE)	P value
OD (mm)	17.66 (0.42)	17.77 (0.44)	0.11 (0.10)	0.28
OS (mm)	17.11 (0.45)	17.17 (0.47)	0.06 (0.10)	0.51
Exophthalmometry measurements: change from first visit to last visit				
	First Mean (SE)	Last Mean (SE)	Change Mean (SE)	P value
OD (mm)	17.90 (0.49)	17.83 (0.47)	-0.07 (0.29)	0.83
OS (mm)	17.45 (0.49)	17.27 (0.49)	-0.18 (0.27)	0.52

Table 5: Exophthalmometry measurements

The average time interval to next follow up was 9.4 weeks and the average time interval to next injection was 17.75 weeks. Approximately one third of patients received radioactive iodine treatment for their systemic disease prior to being seen by our service for TED. One third of patients received orbital radiation therapy during their course of treatment. Following the resolution of the active phase of their disease 68% underwent fatty orbital decompression and 55% underwent bony orbital decompression (the majority of these patients overlapping); only 8 patients (14%) underwent strabismus surgery; 64% underwent eyelid surgery.

Discussion

Corticosteroids are widely used in thyroid eye disease (TED), and are well known to cause several ocular side effects. These include increases in IOP, progression and/or formation of cataracts, and reactivation or worsening of infectious processes among others [2,3,6,7]. Many different formulations of steroids of various anti-inflammatory potencies exist. In addition, there are various ways of local delivery of steroids to the eye and peri-ocular tissues. These include topical drops, ointments, sub-Tenon's injections, intracameral

and intravitreal injections and intraocular implants. Some of these vehicles are well known to cause a high degree of IOP increases, sometimes intractable and occasionally necessitating surgical treatment of induced glaucoma [10-13]. Certain topical drops and ointments have been developed and shown to have a reduced IOP elevating effect (e.g. fluorometholone, rimexolone, loteprednol) [14,15]. We have not noted an increase in IOP with our regimen of periocular steroid injections. This study was undertaken to retrospectively examine our data and to confirm our empirical observation.

As noted above, we use a mixture of dexamethasone and betamethasone. Dexamethasone sodium phosphate provides an immediate effect due to its rapid onset and shorter duration of effect [8]. We used a 4 mg/ml solution. The betamethasone solution that we used is supplied as a 50/50 mixture of sodium phosphate, a soluble ester which provides prompt activity, and betamethasone acetate, which is only slightly soluble and affords sustained activity [9]. The dose of this solution is 6 mg/ml. In our clinical experience, the effect of such injections lasts for approximately 4 weeks.

It has been suggested that a 40 mg of triamcinolone injected periorbitally is equivalent to a daily oral dose of 20 mg of prednisone [3]. Our typical mixture of 0.5 ml dexamethasone and 1.0 ml of betamethasone provides a dose equivalent of over 50 mg of prednisone (0.75 mg of betamethasone = 0.75 mg of dexamethasone = 5 mg of prednisone [8]). Therefore 1 mg of both beta- and dexamethasone=6.67mg of prednisone. 1 ml of 6 mg/ml of betamethasone= 40 mg of prednisone and 0.5 ml of 4 mg/ml of dexamethasone=13.3 mg of prednisone). No published reports on the use of such steroid mixture are available. There is a single published case series documenting the use of betamethasone for orbital injections [16,17]. In that study a mixture of betamethasone sodium phosphate and betamethasone dipropionate (7 mg/ml total, 2-4 ml injected at time of treatment) was used to treat cases of acute idiopathic orbital inflammation. Dramatic response was observed within seven days of the injection. Over an up to eight year follow up period two of the forty-seven patients had recurrences. There were no complications reported.

Our primary endpoint was to investigate whether our regimen caused an increase in IOP. IOP did not appear to change in a statistically significant manner following an injection, demonstrating a lack of short-term effect. There was no increase in IOP at the last recorded examination either, demonstrating that there was no long-term effect. The primary reason for injections given in this series was for soft tissue swelling. This was noted to be effective by the patients in two-thirds of cases. Additionally, subjective complaints of diplopia also improved when perimuscular injections were given. Proptosis did not improve or worsen.

This study suggests that orbital steroid injections do not increase IOP and are effective in conjunction with surgical treatment for treatment of TED. However, there are several limitations of the current study. The power is low (small n), and there is varied follow-up time (1 week to >6 months). Some follow-up times may have been too long to truly study the effect of relatively short-acting steroids. Records were also incomplete (IOP and/or secondary variables were not always documented at every visit), and the amount and location of steroid injections varied from patient to patient. In the future, a prospective study may better standardize treatment follow up and dosing of medication.

In summary, periocular steroid injections during the active phase of thyroid eye disease appear to be effective in reducing soft tissue

swelling and do not appear to cause an increase in intraocular pressure.

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