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ORIGINAL RESEARCH

Subcutaneous Injections of Triamcinolone Acetonide for Upper Eyelid Retraction and Swelling Associated with Thyroid Eye Disease: A Retrospective Case Series Study

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Purpose: To evaluate the efficacy of subcutaneous injection of triamcinolone acetonide (SCTA) in treating upper eyelid retraction and swelling in patients with thyroid eye disease (TED).

Patients and Methods: This case series included consecutive patients (aged 16–69 years, monitored from June 2012 to December 2015) with TED-related eyelid symptom and without an enlarged extraocular muscle on magnetic resonance imaging (MRI). SCTA (0.5 mL, 40 mg/mL) was administered to target the orbital fat around the levator palpebrae superioris (LPS) muscle. Patients who did not exhibit improvement after the first trial received an additional injection. Follow-up was conducted for 12 months with 3-month intervals. Eyelid retraction, eyelid swelling, and eyelid lag were evaluated at each follow-up visit.

Results: In total, 116 eyelids of 102 patients were analyzed. SCTA led to significant improvement in 93% of eyes (108/116), disappearance of eyelid symptoms (74%, 87%, and 73% in retraction, swelling, and lag, respectively), and improvement of scores (from 1.64 to 0.12, 1.32 to 0.26, and 1.72 to 0.30, respectively). Improvement in eyelid symptoms was observed in eight eyes; however, additional steroid therapy was required in these cases due to the emergence of other extraocular muscle inflammation. Additional injection was required in 39.8% of patients. The clinical activity score was lower in the single SCTA group than in the multiple SCTA group (1.5 vs 0.9; $p < 0.01$). However, the levels of thyroid-stimulating hormone receptor antibody and MRI findings were not significantly different between the two groups. No elevation in intraocular pressure was observed. Eight female patients experienced menstrual disorder.

Conclusion: SCTA effectively reduced LPS muscle enlargement and fat tissue swelling in patients with TED. A single SCTA was sufficient in almost 60% of the patients; nevertheless, follow-up is necessary to detect early signs of orbital inflammation even in eyelid-symptom-improved patients.

Keywords: Graves' disease, triamcinolone injection, magnetic resonance imaging, levator palpebrae superioris muscle, inflammation

Introduction

Thyroid eye disease (TED), also termed Graves' ophthalmopathy, is an autoimmune disorder that affects the eyes of individuals with hyperthyroidism or Graves' disease. TED develops more commonly in females than in males (16 vs 2.9 cases per 100,000 individuals).[1,2] The most common symptoms of TED include proptosis, double vision, eyelid swelling, and sensitivity to light. TED is caused by an autoimmune reaction, in which the immune system attacks the muscles and other tissues around the eyes. Upper eyelid retraction and swelling are frequent symptoms in patients with TED.[3,4] The incidence rates of eyelid retraction and swelling in patients with TED are 58–98% and 47%–75%, respectively.[4,5] The

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age of patients with upper eyelid retraction and swelling mostly ranges from 20 to 50 years.[4] Therefore, the appearance of such retraction and swelling causes cosmetic discomfort.[6,7]

It is believed that the underlying cause of the autoimmune reaction in TED is related to Graves' disease. Production of excess thyroid hormones may lead to overstrain and subsequent malfunction of the Mueller's muscle in the upper eyelid, resulting in lid retraction.[8] Another potential mechanism involved in this process is inflammation of the levator palpebrae superioris (LPS) muscle. It has been suggested that inflammation of the LPS muscle is induced by antithyroid autoantibodies, namely, thyroid-stimulating hormone receptor antibodies (TRAb) and thyroid-stimulating antibodies (TSAb).[9,10]

Various approaches have been utilized to treat the abovementioned conditions. An α-adrenergic blocker ophthalmic solution is effective against hypertonia in the Mueller's muscle; however, it remains ineffective against inflammation of the LPS muscle.[11] Botulinum toxin injections are used to resolve upper eyelid retraction; however, this treatment modality requires regular application.[12] Although steroid pulse therapy is an effective treatment option, it is associated with some side effects, including diabetes and hyperlipidemia.[13] Surgical treatments have also been performed in this setting; however, surgeries can occasionally lead to unexpected outcomes, including over/under-correction and formation of the undesirable double eyelid line.[14]

It has been reported that subconjunctival injection of triamcinolone acetonide (TA) targeting the Mueller's muscle is effective in reducing upper eyelid retraction in the early congestive stage in patients with TED.[15–18] We previously reported the Effectiveness of subcutaneous injection of triamcinolone acetonide (SCTA) targeting the LPS muscle and surrounding orbital fat in three cases.[19] However, several aspects of SCTA (such as efficacy, sufficiency of a single injection, and duration) remain unclear. In this study, we investigated the efficacy of SCTA targeting the LPS muscle and surrounding orbital fat in reducing upper eyelid retraction and swelling in a series of patients with TED.

Patients and Methods

Patients

In this study, consecutive 102 Patients (aged 16–69 years) diagnosed with TED were recruited between June 2012 and December 2015. Inclusion criteria were as follows: upper eyelid retraction or eyelid swelling and inflammatory hypertrophy of the LPS muscle on magnetic resonance imaging (MRI). Exclusion criteria were as follows: patients with other extraocular muscle hypertrophy and strabismus; those with a history of eyelid or orbital surgery; those who received injections or oral steroids prior to the first visit; and those with diabetes.

All patients experienced both upper eyelid retraction and swelling (unilaterally or bilaterally) and had LPS muscle hypertrophy and inflammation, as demonstrated by MRI (Achieva1.5T, Philips Japan). At the first visit, the thyroid function was normal for all patients regardless of medication use. Treatment was initiated within 6 months of the appearance of TED signs. MRI findings of LPS muscle enlargement were considered based on an area of >0.17 cm^2 and an inflammation with a T2 signal intensity ratio of >1.0. Patients with an enlarged extraocular muscle on MRI were excluded from the analysis.

SCTA

SCTA was administered as previously described.[19] Prior to SCTA, the upper eyelid was cooled with an ice pack for 1 min to minimize pain and subcutaneous bleeding. Patients had a downward gaze in the supine position, and the upper eyelid skin was pulled. A 26-gauge needle was inserted into a depth of ~1 cm. After confirming the absence of blood reflux, 0.5 mL of TA (40 mg/mL) was injected to target the orbital fat around the LPS muscle. A single SCTA was administered to each eyelid. Follow-up was conducted every 3 months for a total of 12 months. Patients who did not exhibit improvement at follow-up visits received an additional injection.

Measurements

At each visit, the following eyelid symptoms were clinically evaluated using a four-grade scale: upper eyelid retraction, upper eyelid swelling, and eyelid lag (Supplementary File 1). Upper eyelid retraction was evaluated by measuring the palpebral fissure height as well as determining the presence of scleral show. Eyelid swelling was assessed depending on the presence of eyelid bulging from the upper eyelid margin and the lack of an upper eyelid sulcus (Figure 1). In addition,

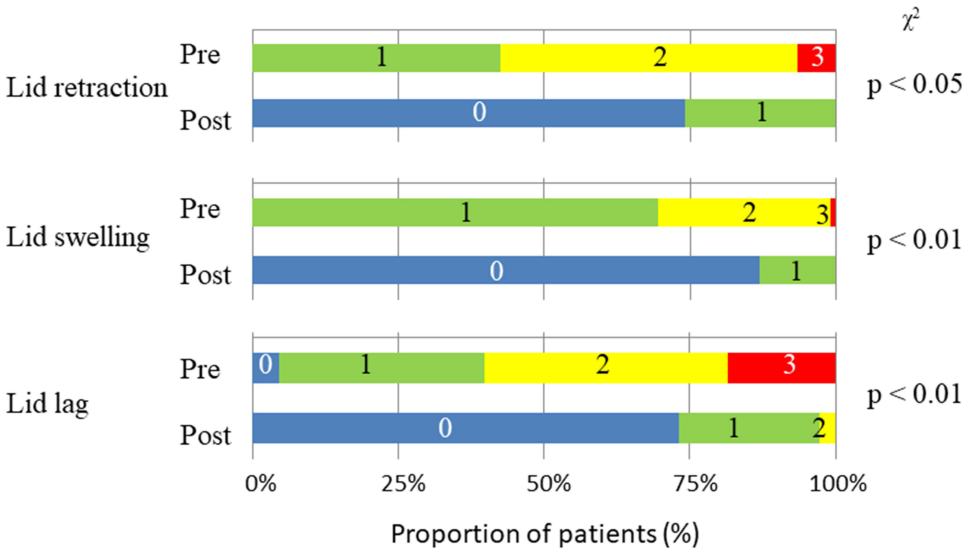

Figure 1 Change of eyelid scores. Pre and Post indicate before and after subcutaneous injections of triamcinolone acetonide, respectively.

the LPS muscle and orbital fat tissue were observed using MRI before and at 6 or 8 months after treatment. LPS muscle enlargement and fat swelling were assessed using T1-weighted sagittal images, and inflammatory edema in the LPS muscle was visually assessed using T2-weighted images of fat suppression and quantitatively measured using T2 relaxation time. Upper eyelid swelling was evaluated based on the orbital fat around the LPS muscle and the retro-orbicularis oculi fat thickness on sagittal MRI. To assess the risk of TA-induced complications,[15–17] intraocular pressure was measured before and at 1, 3, 6, and 12 months after treatment. For safety, a post-administration interview was conducted among patients to determine the presence of menstrual irregularities and internal bleeding. They were also visually examined to check for the presence of subcutaneous hemorrhage and appearance of TA opacities under the skin. Long-term side effects were evaluated via visual examination to confirm the presence of ptosis and measurement of eyelid cleft height at the time of consultation.

The clinical activity score (CAS), based on the 2021 European Group on Graves' orbitopathy[20] clinical practice guidelines, was evaluated at each visit for 1 year after the first SCTA. The CASs were determined between January 2012 and December 2016. In addition, we measured the titers of TRAb and TSAb before SCTA. The testing was outsourced to a laboratory (BML Inc. Japan), and the tests were performed using DYNO test TRAb Human kit YAMASA (Kawasaki, Japan) for TRAb and the enzyme immune assay for TSAb.

MRI Assessment

Prior to treatment, the cross-sectional area of the maximum thickening of the LPS muscle was measured using a coronal section. The signal intensity ratio was calculated by dividing the T2 relaxation time of the LPS muscle by that of cerebral white matter.

Endpoints

The scores for upper eyelid retraction, upper eyelid swelling, and eyelid lag before and at 12 months after SCTA were evaluated. The correlations of therapeutic efficacy with each CAS, antithyroid autoantibodies (TRAb and TSAb), and MRI findings were investigated.

Continuous variables were expressed as means and standard deviations, while categorical valuables were expressed as numbers and percentages. Data were compared using the Student's *t*-test or chi square test via JMP® software 11 (Tokyo, Japan).

Ethics Statement

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and other regulatory requirements. This study was assessed by the Institutional Review Board (Review board of Meiwa Hospital, No. 201207-

Table 1 Patient Demographics

Age (years)		Mean: 39.8 (range: 16–69)
Sex	Male	7 patients (6.9%) 8 eyes (6.9%)
	Female	95 patients (93.1%) 108 eyes (93.1%)
LPS muscle enlargement		116 eyes (100.0%)
Inflammation of the LPS muscle		116 eyes (100.0%)
TSAb		819.8% ± 777.4% (range: 97–4206%)
TRAb		21.7 ± 22.2 (range: 0.1–82.5) IU/L
Smoking		18 patients (17.6%)

Abbreviations: LPS, levator palpebrae superioris; TRAb, thyroid-stimulating hormone receptor antibodies; TSAb, thyroid-stimulating antibodies.

1 at 2012) for ethical, scientific, and medical/pharmaceutical rigor. Written informed consent was obtained from the patients for publication of these case reports and accompanying images.

Results

In total, 116 eyelids of 102 patients (males: n = 7, 8 eyelids; females: n = 95, 108 eyelids) were analyzed. Patient demographics are presented in Table 1. The average patient age was 39.8 (range: 16–69) years. Patients who received radioisotope therapy were also included.

Effectiveness

At 12 months after the initial SCTA, the eyelid symptoms disappeared in 55% of eyes (64/116) and improved in 45% of eyes (52/116). However, 7% (8/116) of the eyes required systemic steroid pulse therapy due to worsening of TED; appearance of diplopia during the 12-month follow-up, and inflammatory hypertrophy of the external ocular muscles on MRI, whereas eyelid symptoms improved. Significant improvement was observed in 93.1% of the eyes (108/116 eyes; 95/102 patients) after treatment with SCTA only (average: 1.6 injections). A single SCTA was sufficient to induce improvement in 60.2% of the eyes (65/108), though an additional injection was required for 39.8% of the eyes (43/108) (Figure 2).

Following SCTA, eyelid retraction, swelling, and lag disappeared in 74.0%, 87.0%, and 73.1% of patients, respectively, and the corresponding scores improved from 1.64 to 0.12, 1.32 to 0.26, and 1.72 to 0.30 (ie, before and after SCTA, respectively). T2 relaxation times of the LPS muscle were significantly reduced from 57.1 ± 12.1 (range: 44.78–96.99) to 52.1 ± 8.0 (range: 43.21–97.07) ms (P = 0.0021, Wilcoxon signed-rank test). The demographics of patients

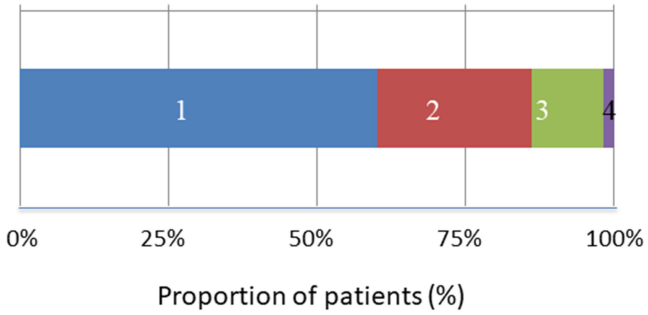

Figure 2 Number of subcutaneous injections of triamcinolone acetonide (SCTA). Patients without improvement (after 2 or 3 months from the first trial) received an additional SCTA. The mean number of administrations was 1.6.

receiving additional steroid therapy are shown in Table 2. There was no significant difference in the background information of patients who received or did not receive additional steroid therapy (Table 3).

The association between the number of administrations and background factors is shown in Table 4. Only the CAS was significantly lower in the single SCTA group than in the multiple SCTA group (1.5 vs 0.9; $p < 0.01$; Student's *t*-test). However, the evaluation of TRAb levels and MRI findings did not yield significant Results. During the worsening of TED, TSAb levels were elevated only in four cases.

MRI revealed that the area of LPS and T2 signal intensity ratio were not significantly different between single and multiple SCTA groups.

Multivariate logistic regression analysis with single or multiple SCTA as a variable and TSAb, smoking, area of LPS before first SCTA, and signal intensity ratio of LPS before first SCTA as associated factors revealed no significant relationship between the factors and treatment.

Table 2 Demographics of Patients Receiving Additional Steroid Therapy

Case No.	Age, Sex	Time Since Appearance of TED	Internal Medicine	History of Treatment	TSAb Before SCTA	TSAb at 6–12 Months
1	44, female	3 months	T4	RI + thyroidectomy	2758	7028*
2	44, female	9 months	None	Thyroidectomy for cancer	257	1045*
3	45, female	1 month	MMI 25 mg	–	789	803
4	38, female	2 months	No	–	143	138
5	41, female	6 months	PTU 150 mg	–	3837	5207*
6	47, female	1 month	KI	–	1677	4398*
7	46, female	4 months	MMI 30 mg	–	2162	2242

Note: *Indicates the number of cases in which TSAb levels were increased compared with those before initial SCTA (Student's *t*-test).
Abbreviations: RI, radioisotope therapy; KI, potassium iodide; MMI, thiamazole; PTU3, propylthiouracil; SCTA, subcutaneous injection of triamcinolone acetonide; T4, thyroxine; TED, thyroid eye disease; TSAb, thyroid-stimulating antibody.

Table 3 Comparison of the Background Information of Patients Treated with TA Only and Those Who Received Additional Treatment

	Treated with SCTA Only	Required Additional Therapy	P values (Student's t-test)
Age (years)	39.6	43.6	0.1309
Area of the LPS muscle (cm^2)	0.28	0.25	0.5819
LPS T2SIR	1.20	1.30	0.1527
Time since symptom onset (months)	5.5	3.7	0.3692
CAS	1.1	1.6	0.2238
TSAb (%)	977	1660	0.1722
TRAb (IU/L)	8.0	13.3	0.2701

Abbreviations: CAS, clinical activity score; LPS, levator palpebrae superioris; T2SIR, signal intensity ratio of T2-relaxation time; SCTA, subcutaneous injection of triamcinolone acetonide; TRAb, thyroid-stimulating hormone receptor antibody; TSAb, thyroid-stimulating antibody.

Table 4 Comparison of the Background Information of Patients Receiving Single and Multiple SCTA

	Single SCTA	Multiple SCTA	P values (Student's *t*-test)
Age (years)	38.9	40.6	0.5063
Area of the LPS muscle (cm^2)	0.28	0.29	0.2311
LPS T2SIR	1.19	1.22	0.5904
Time since symptom onset (months)	5.7	5.1	0.3692
CAS	0.9	1.5	*0.0008*
TSAb (%)	1023	903	0.6846
TRAb (IU/L)	8.2	7.8	0.6763

Abbreviations: CAS, clinical activity score; LPS, levator palpebrae superioris; T2SIR, signal intensity ratio of T2 relaxationa time; SCTA, subcutaneous injection of triamcinolone acetonide; TRAb, thyroid-stimulating hormone receptor antibody; TSAb, thyroid-stimulating antibody.

Safety

No severe complications occurred during this study, and elevation in intraocular pressure was not observed in any of the patients. Eight female patients experienced menstrual disorder. Moreover, none of the patients showed dosing position error.

Discussion

In this case series, we investigated the efficacy and Safety of SCTA in consecutive patients with TED. The results showed that SCTA improved eyelid symptoms in almost 80% of patients without severe complications or elevation in intraocular pressure. However, SCTA induced menstrual disorder in some female patients.

Numerous studies have described the sensitivity of TED to steroid therapy. Currently, corticosteroids are commonly used in the treatment of TED to reduce inflammation and swelling in the eyes and surrounding tissues. Several studies have shown that steroid therapy can effectively improve TED symptoms. However, the response to steroid therapy can vary among individuals, and some patients may not respond to steroids or might experience treatment-related side effects.[15–17] In addition, long-term use of steroids can exert negative side effects on other organs of the body. Therefore, it is important to carefully monitor patients receiving steroid therapy for TED.

Eyelid findings of less than CAS3, as observed in this study, are not an indication for steroid pulse therapy. However, patients may desire treatment of dry eyes and facial changes caused by eyelid symptoms. Patients may benefit from the availability of a less physically demanding and more convenient treatment option of anti-inflammatory topical injections rather than eye drops, ointments, or surgery. Furthermore, subconjunctival injections are easily administered, and IOP checks are easily implemented in daily practice by ophthalmologists (although this may be difficult for physicians not specializing in ophthalmology). Conversely, subcutaneous injections that do not require IOP checks may be easily administered by physicians who are not ophthalmologists.

In contrast to transconjunctival administration of TA, SCTA administration did not induce adverse events or elevation in intraocular pressure in this study. The method used for SCTA administration was simpler than that for transconjunctival administration. Moreover, the efficacies of these two approaches were similar, ranging 68%–93%. According to the results of the abovementioned reports,[15–19] SCTA is safer, easier, and almost as efficacious as transconjunctival administration. Nevertheless, a disadvantage of SCTA is the presence of residual TA in subcutaneous tissue, which is determined by its visible white color. In this study, there was no residual TA in any of the patients. The elimination of TA in subcutaneous tissue may be responsible for the difference in the administration depth in the current study compared with that reported in previous studies.[19] In this study, no dosing position error was noted. Therefore, we confirmed that

SCTA administration at a point where the needle (1 cm) is no longer visible can help avoid TA release immediately below the skin.

The CAS was lower in the single SCTA group than in the multiple SCTA group. However, TRAb levels and MRI findings were not significantly different between the two groups. TRAb levels were correlated with the severity of TED.[21,22] However, in the present study, patients with only eyelid symptoms were not considered to have severe thyroid ophthalmopathy and were classified as mild cases. Therefore, it is possible that the number of injections did not correlate with autoantibody levels because some patients did not have high antibody levels prior to the treatment.

A single SCTA proved curative in 60% of the patients, while 93% of eyes were improved with injections every 3 months. In previous studies, researchers have administered topical injections each month; however, as frequent administration of steroids is also linked to an increase in side effects, administration at 3-month intervals was considered safe and sufficiently effective.[15–17] Although eyelid symptoms improved, diplopia appeared in seven patients during the course of the study. Eyelid symptoms are often observed early during the course of TED. In some cases, ophthalmopathy occurs with eyelid symptoms alone, whereas in other cases, external ocular muscle hypertrophy appears along with eyelid symptoms.

In these cases, the levels of autoantibodies increased during the course of the disease or remained positive without decreasing. Hence, it is believed that the development of orbital inflammation is accompanied with a relapse or worsening of a primary disease, such as Graves' disease. Thus, follow-up of ocular symptoms is necessary even after improvement in eyelid symptoms. In particular, MRI verification is strongly recommended in patients exhibiting positivity for autoantibodies.

SCTA may induce an elevation in blood glucose levels. We did not examine blood glucose levels because patients with diabetes mellitus were excluded from this study. Monitoring of blood glucose levels is recommended for patients with diabetes.

Conclusion

SCTA, even when administered as a single injection, may be an effective treatment option for improving upper eyelid retraction and swelling associated with TED in the inflammatory LPS muscle enlargement stage. This injection is easy to administer, and certain untoward effects linked to this approach tend to resolve spontaneously. We recommend using MRI to determine the presence of inflammation. Some patients progressed into extra muscle enlargement after levator muscle enlargement. Therefore, follow-up observation is necessary to avoid overlooking orbital inflammation worsening, even in patients who showed improvement in eyelid symptoms.

We recommend this local injection because it is simple, inexpensive, and effective for localized inflammation in patients with only eyelid findings and CAS <3.

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Disclosure

The authors report no conflicts of interest related to this work.

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