Triamcinolone acetonide injection in the treatment of upper eyelid retraction in Graves’ ophthalmopathy evaluated by 3.0 Tesla magnetic resonance imaging

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**Purpose:** To evaluate changes in the levator palpebrae superioris (LPS) muscle on 3.0 T magnetic resonance imaging (MRI) after triamcinolone acetonide injection for treating upper lid retraction (ULR) with Graves’ ophthalmopathy (GO) and to explore the value of LPS muscle quantitative measurement for clinical treatment.

**Methods:** Patients with GO showing ULR were studied retrospectively and they underwent 3.0 T MRI scans before and after subconjunctival injection of triamcinolone acetonide. The largest thickness (T) and highest signal intensity (SI) of LPS muscle on the affected eyes were measured in the sequences of coronal T2-weighted, fat-suppressed fast spin echo imaging (T2WI-fs) and T1-weighted, fat-suppressed, contrast-enhanced fast spin echo imaging (T1WI-fs + C), respectively. The SI ratio (SIR) (LPS muscle SI/ipsilateral temporalis SI) was calculated individually. Depending on the therapeutic effect, patients were divided into effective group and non-effective group. Independent t-test was used to compare SIR and T of LPS muscle in different treatment groups before treatment, and paired sample t-test was used to compare SIR and T of LPS muscle before and after treatment. Then cut-off level for predicting therapeutic effect and the receiver operating characteristic curve (ROC) curve were analyzed. **Results:** Sixty-two patients (77 eyes) were enrolled. After treatment, the T of LPS muscle showed significant decrease in all sequences in both effective and non-effective treatment groups. However, changes in SIR of LPS muscle in the two groups were different; SIR of LPS muscle on T2WI-fs and T1WI-fs + C decreased after treatment in the effective group (P < 0.05) and SIR of LPS muscle showed no statistically difference in all sequences (all P > 0.05) in the non-effective group. There was a correlation between SIR of LPS muscle before treatment and after treatment with triamcinolone acetonide injection, which was that the SIR of LPS muscle in the effective treatment group was lower than that in the non-effective treatment group on T1WI-fs + C (P < 0.001). SIR of LPS muscle on T1WI-fs + C showed 87.5% sensitivity and 66.7% specificity to predict therapeutic effect (area under the ROC curve [AUC] = 0.840). **Conclusion:** In GO patients with ULR, 3.0 T MRI can be used to evaluate the response of triamcinolone acetonide injection. SIR of LPS may be a predictor of its efficacy.

**Key words:** Graves’ Ophthalmopathy, levator palpebrae superioris muscle, MRI, upper lid retraction

Graves’ ophthalmopathy (GO) is a common complication of Graves’ disease and is one of the most common eye diseases and blinding diseases in adults.1,2 GO has two basic course stages of development: active phase and inactive or chronic phase. The main clinical symptoms are eye impairments of different degrees, and upper lid retraction (ULR) is one of the common clinical symptoms.3 The pathogenesis is not clear, but most studies showed that the immunoreactive inflammation of levator palpebrae superioris (LPS) muscle is the main cause of early ULR. In chronic phase, LPS muscle and Müller muscle undergo fibrosis and adhere to the surrounding orbital tissues, resulting in irreversible ULR.4 Upper lid retraction affects the facial appearance and is easy to be accompanied by eye diseases. Therefore, the timely and effective treatment of ULR has important clinical significance.5 Recently, some studies have found that subconjunctival injection of glucocorticoids is a relatively safe and effective treatment for GO’s early ULR.6 However, the treatment time and follow-up time are long, so it is necessary to monitor the condition and evaluate the curative effect in time, so as to adjust the treatment method at any time or even carry out surgical intervention treatment. Repeated subconjunctival injection may cause upper eyelid stiffness and affect the later surgical effect.7 There is lack of treatment

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evaluation methods in the clinic, and it is urgent to find new effective and accurate quantitative evaluation methods to estimate the therapeutic effect.

Previous studies have shown that magnetic resonance imaging (MRI) is one of the most effective examination methods for diagnosing GO and evaluating its active phase and response to treatment. At present, there are many studies on the application of MRI in the diagnosis and treatment of GO, but there is no study on the treatment response of GO patients whose main symptom was ULR. Therefore, this study is based on the signal characteristics of LPS muscle of GO patients with ULR in 3.0T MRI examination, to analyze the relationship between the change of LPS muscle and the effect of subconjunctival injection of triamcinolone acetonide.

**Methods**

**Subjects**

Patients were prospectively enrolled from Peking Union Medical College Hospital (Beijing, China) from May 2017 to May 2019. This study was approved by the Ethics Committee of Peking Union Medical College Hospital, and all patients signed informed consent.

The patients fulfilled the following inclusion criteria: mild to moderate GO with features of either unilateral or bilateral lid retraction; clinical activity score (CAS) ≤ 3; stable thyroid function; age of 18 years or older; absence of other systemic disease; absence of myopathy, severe proptosis, optic neuropathy, corneal ulcer, and recent glucocorticoid administration. Exclusion criteria were previous treatment for GO with steroids or radiation and patients with compressive optic neuropathy.

All patients received treatment with continuous, regular, intermittent, repeated subconjunctival triamcinolone acetonide injection for 3 months in the Department of Ophthalmology, Peking Union Medical College Hospital. Triamcinolone acetonide solution (Kunjing Jida Pharmaceutical Co., Ltd., China) in a volume of 0.5 ml (40 mg/ml) was injected into the subconjunctival area, 5 mm above the upper edge of the everted tarsus. The treatment was repeated monthly and stopped if the retraction completely resolved. The patients were treated less than 10 times. The marginal reflex distance (MRD) of the upper eyelid margin was measured by the ophthalmologist before subconjunctival triamcinolone acetonide treatment and every 1, 2, 3, 6 months, and 1 year or more of clinical follow-up. All the patients received 3.0 T orbital enhanced MRI before treatment.

All patients received a 3.0 T orbital MRI before treatment and at least 6 months after the end of treatment. According to the change of the MRD before and after treatment, patients were divided into two groups based on the therapeutic effect: effective group and non-effective group (when the MRD decreased ≥ 2 mm, the treatment was considered effective; when the MRD decreased < 2 mm, the treatment was considered ineffective).

**MR Scan Protocol**

Before and after treatment, orbital MRI was performed using a 3.0 T magnetic resonance scanner (GE Signa VH/i EXCITE II 3.0T; General Electric Medical Systems, Milwaukee, WI, USA) with a head coil. MRI was performed with coronal T1-weighted, fat-suppressed fast spin echo (T1W-fs) and T2-weighted, fat-suppressed, fast spin echo (T2W-fs) images. Gadopentetate dimeglumine (Gd) (10 ml: 4.69 g) was injected (magnetic

phenylamine; Beijing Hokuriku Pharmaceutical Co., Ltd, China) into the upper limb veins according to the weight of each patient (0.2 ml/kg). Contrast-enhanced images with T1-weighted fat suppression (T1W-fs + C) were obtained, consisting of axial, coronal, and sagittal images (on a plane parallel to the optic nerve). The imaging parameters included the following:

- **T1WI-fs**: time of repetition (TR) 1000 ms, time of echo (TE) 98.3 ms, matrix 256 × 256, number of excitations (NEX) 2, field of view(FOV) 20 cm × 15 cm, layer thickness 3.0 mm, layer spacing 0.5 mm.
- **T2WI-fs**: TR 3480 ms, TE 118.3 ms, matrix 256 × 256, NEX 2, FOV 20 cm × 15 cm, layer thickness 3.0 mm, layer spacing 0.5 mm.
- **T1WI-fs + C**: TR 8.4 ms, TE 4.0 ms, matrix 256 × 224, NEX 1, FOV 18 cm × 16 cm, slices thickness 3.0 mm, layer spacing 0.5 mm, and a total of 16 layers of images.

**Image Analysis**

All image data were transmitted to the picture archiving and communication system (PACS) workstation. Two radiologists with 5 and 10 years of experience in head and neck imaging (Duan M. and Chen Y.) were blinded to the clinical diagnosis and they measured the pre- and post-treatment largest thickness dimension (T) and the highest signal intensity (SI) of LPS muscle after scanning the coronal T2WI-fs and T1WI-fs + C, respectively. The region of interest (ROI) measuring the SI included the extraocular muscle cross section as much as possible, but did not exceed the edge of LPS muscle [Fig. 1]. At the same time, the SI at the highest position of the ipsilateral temporalis signal was measured. Both T and SI were measured three times and averaged. Then SI ratio (SIR) between the LPS muscle and ipsilateral temporalis was calculated, respectively. SIR = SI of LPS muscle/SI of the ipsilateral temporalis. SIRs of LPS muscle before and after treatment were labeled as SIRb and SIRa, T values of LPS muscle before and after treatment were marked as Tb and Ta, respectively.

**Statistical Analysis**

Statistical analysis was performed using statistical package for the social sciences (SPSS) 19.0 statistical software (IBM SPSS, version 19.0; SPSS Inc., Chicago, IL, USA). Data entry was entered and verified using EpiData 3.0 dual track. Intraclass correlation coefficient (ICC) was used to evaluate the consistency of the two radiologists. The measurement data were expressed as mean ± standard deviation (SD), and after normality test and homogeneity test of variance, SIR and T of LPS muscle before and after treatment were compared using paired sample t-test. P values in T2WI-fs and T1WI-fs + C were labeled as Pa and Pbc, respectively. P < 0.05 was considered statistically significant.

**Results**

**Participants**

The enhanced MR examination was carried out in 66 patients, and four patients were excluded because their MR images had severe motion artifacts, and therefore, they could not be evaluated. Finally, 62 patients with 77 eyes of ULR were included in the study. Among the 62 patients, 47 patients with 56 eyes were classified as effective group (male: female = 4:43, mean age 32.3 ± 7.1 [22–47] years) and 15 patients with 21 eyes were classified as non-effective group (male: female = 2:13,
mean age 35.8 ± 6.6 [27–49] years) [Fig. 2]. There was no significant difference in gender ($P = 0.639$) and age ($P = 0.098$) between the effective group and the non-effective group. All the patients suffered from hyperthyroidism, and the duration of hyperthyroidism was 7.83 ± 5.2 (1–24) months. The mean lid retraction time at the first examination was 6.5 (1–24) months. Thyroid status was stable in this study. There was no significant difference in time of abnormal thyroid function ($P = 0.981$) and time of ULR ($P = 0.398$) between the effective group and the non-effective group.

**T and SIR Measurements of Extraocular Muscle**

The consistency results of the two radiologists showed that the ICC was relatively high (ICC > 0.900) before and after treatment [Table 1].

**T and SIR Measurement of LPS Muscle Before and After Treatment in Effective and Non-effective Groups**

Forty-one patients (53 eyes) received enhanced MRI after treatment. Among them, 29 patients (37 eyes) were in the effective group and 12 patients (16 eyes) were in the non-effective group.

In the effective group, compared with before treatment, T and SIR of LPS muscle were decreased on T2WI-fs and T1WI-fs + C after treatment, and the difference was statistically significant (all $P < 0.001$). In the non-effect group, compared with before treatment, T of LPS muscle was decreased on T2WI-fs and T1WI-fs + C after treatment, and the difference was statistically significant ($P_{T2} < 0.05, P_{T1-C} < 0.005$). However, SIR of LPS muscle showed no statistical significance (all $P > 0.05$) [Table 2].

### Table 1: Consistency analysis of T and SIR of LPS between the two radiologists before and after treatment

| LPS muscle | Sequence | SIR/T | ICC  | 95% CI       |
|------------|----------|-------|------|--------------|
| Before treatment | T2WI-fs | SIR 0.991 (0.984, 0.995) | T 0.993 (0.988, 0.996) | T1WI-fs + C SIR 0.995 (0.992, 0.997) | T 0.941 (0.900, 0.965) |
| After treatment | T2WI-fs | SIR 0.965 (0.932, 0.982) | T 0.933 (0.873, 0.965) | T1WI-fs + C SIR 0.966 (0.934, 0.983) |

CI = confidence interval, ICC = intraclass correlation, LPS = levator palpebrae superioris, SIR = signal intensity ratio, T = thickness, T1WI-fs + C = T1-weighted, fat-suppressed, contrast-enhanced fast spin echo imaging, T2WI-fs = T2-weighted, fat-suppressed fast spin echo imaging.

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**Note:** $n_0$: for the number of patients, $n_e$: for the number of affected eyes.

**Figure 2:** Patient selection and MR evaluation flowchart MR = magnetic resonance

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**Figure 1:** An example of extraocular muscle measurement. On contrast-enhanced, T1-weighted image, T values were acquired at the thickest slice of LPS muscle (a, T). Signal intensity was acquired from the maximum area of the LPS muscle (b, ROI) LPS = levator palpebrae superioris, ROI = region of interest.
Changes of the right upper lid retraction and MRI imaging of the patients in the effective and non-effective group [Figs 3 and 4].

Analysis of T and SIR of LPS Muscle Before Treatment Between Effective and Non-effective Groups

Among the 62 patients with 77 abnormal eyes, LPS muscle of the effective group showed a significantly lower SIR on T1WI-fs + C (P < 0.001) compared to the non-effective group [Table 3].

ROC Curve Analysis

The area under the ROC curve (AUC) of SIR of LPS muscle on T1WI-fs + C before treatment was 0.840 (P < 0.05). With SIR ≤ 1.56 as the cut-off point, the sensitivity was 87.5% (49/56), specificity was 66.7% (14/21), positive predictive value was 87.5% (49/56), negative predictive value was 66.7% (14/21), and the Youden index was 54.2% [Fig. 5].

Discussion

This is the first study to analyze the SI characteristics of LPS muscle in GO patients based on orbital contrast-enhanced MRI and to discuss the correlation between the signal characteristics of LPS muscle and the efficacy of subconjunctival injection of triamcinolone acetonide.
Some previous studies have found that the characteristics of extraocular muscle signals in MRI have a predictive value in GO’s glucocorticoid therapy.\(^\text{[14]}\) Also, 3.0 T MRI has the characteristics of higher signal-to-noise ratio, spatial resolution, fast scanning speed, and better enhancement effect. Increased signal in T2WI indicated extraocular muscle inflammatory cell infiltration, edema, and muscle swelling, while decreased signal indicated extraocular muscle fiber hyperplasia.\(^\text{[17]}\) The inflammatory response of extraocular muscles was found more clearly in contrast-enhanced T1WI and was helpful to find the location of inflammation in extraocular muscle. Some studies have pointed out that contrast-enhanced T1WI is a useful tool for detecting inflammation of extraocular muscles in GO. This is due to the inflammatory changes in the extraocular muscles of GO patients and the increased intramuscular blood vessels, which are significantly enhanced on contrast-enhanced T1WI sequence.\(^\text{[18]}\)

In our study, we found that SIR value of LPS muscle on T1WI-\(fs\) + C in the effective group was lower than that in the non-effective group. This shows that patients with poor treatment effect have more severe inflammation in the LPS muscle. This was inconsistent with other study results; for example, Jiang et al.\(^\text{[14]}\) study found that the more severe the extraocular muscle edema before treatment, the more obvious the reduction of edema after immunosuppressive treatment and the more significantly the clinical symptoms improved. The reasons may be as follows: 1) patients in the non-effective group were prone to experiencing more severe immunoreactive inflammation than those in the effective group. Also, the inflammation lasted longer in the non-effective group. For these types of patients, the treatment plan of this study might not be sufficient to achieve normal lid positions. Further studies regarding the optimal dosage, injection volume, and injection intervals should be conducted in the future. 2) GO patients in previous studies were reported to have higher CAS scores mainly involving the inferior rectus muscle and medial rectus muscle.\(^\text{[14]}\) Our study is for patients with ULR as the main symptom and showing LPS muscle involvement. In our study, patients were found to have lower CAS scores. Meanwhile, this study found that there was no significant difference in the T of LPS muscle on T2WI-\(fs\) and T1WI-\(fs\) + C in different treatment effect groups before treatment, indicating that the degree of LPS muscle thickening is not a main factor to predict the treatment effect of ptosis.

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**Table 2: T and SIR of LPS before and after treatment in both groups (mean±SD, mm)**

| Groups             | Sequence       | SIR/T | Before treatment | After treatment | T     | P       |
|--------------------|----------------|-------|------------------|----------------|-------|---------|
| Effective group    | T2WI-\(fs\)    | SIR   | 1.73±0.57        | 1.36±0.31      | 4.123 | 0.000   |
|                    | T              |       | 2.33±0.81        | 1.62±0.60      | 5.392 | 0.000   |
|                    | T1WI-\(fs\) + C| SIR   | 1.40±0.38        | 1.19±0.28      | 4.058 | 0.000   |
|                    | T              |       | 2.93±0.99        | 1.98±0.60      | 6.35  | 0.000   |
| Non-effective group| T2WI-\(fs\)    | SIR   | 1.89±0.67        | 1.73±0.35      | 1.431 | 0.059   |
|                    | T              |       | 2.42±1.20        | 1.81±0.73      | 3.097 | 0.009   |
|                    | T1WI-\(fs\) + C| SIR   | 1.59±0.40        | 1.49±0.37      | 1.796 | 0.121   |
|                    | T              |       | 2.59±0.98        | 1.98±0.86      | 4.321 | 0.001   |

LPS=levator palpebrae superioris, SD=standard deviation, SIR=signal intensity ratio, T=thickness, T1WI-\(fs\)+C = T1-weighted, fat-suppressed, contrast-enhanced fast spin echo imaging, T2WI-\(fs\)=T2-weighted, fat-suppressed fast spin echo imaging

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**Table 3: T and SIR of LPS before treatment between effective and non-effective groups (mean±SD, mm)**

| Extracocular muscles | Sequence       | SIR/T | Effective group (\(n=56\)) | Non-effective group (\(n=21\)) | T     | P       |
|----------------------|----------------|-------|-----------------------------|---------------------------------|-------|---------|
| Levator palpebrae    | T2WI-\(fs\)    | SIR   | 1.73±0.46                   | 1.97±0.77                       | −1.640| 0.214   |
|                      | T              |       | 2.23±0.59                   | 2.44±1.11                       | −1.254| 0.015   |
|                      | T1WI-\(fs\) + C| SIR   | 1.34±0.21                   | 1.81±0.44                       | −4.467| 0.000   |
|                      | T              |       | 2.59±0.75                   | 2.73±1.32                       | −0.724| 0.367   |

LPS=levator palpebrae superioris, SD=standard deviation, SIR=signal intensity ratio, T=thickness, T1WI-\(fs\)+C = T1-weighted, fat-suppressed, contrast-enhanced fast spin echo imaging, T2WI-\(fs\)=T2-weighted, fat-suppressed fast spin echo imaging

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**Figure 5:** ROC curve of SIR of the LPS muscle on T1WI-\(fs\) + C predicts therapeutic effect before treatment LPS = levator palpebrae superioris, SIR = signal intensity ratio, T1WI-\(fs\)+C = T1-weighted, fat-suppressed, contrast-enhanced fast spin echo imaging.
In a previous study, T2WI-fs was used to indicate the activity stage in GO.[17] However, in our study, T2W SIR of LPS muscle showed no significant difference between the effective group and non-effective group ($P > 0.05$). The reasons may be as follows: 1) The $T$ of LPS muscle is relatively small. The space resolution was limited; therefore, SIR of T2WI-fs was affected by partial volume effect. 2) The impact of the measurement of the temporal muscle signal. Some studies indicated that the temporal muscle area in the orbital MR image is relatively narrow, which may contain non-muscle tissue, and the individual variability is large, which resulted in bias of the measured data.[18][20] High-resolution T2 sequences may improve this problem and will be studied in the future.

In addition, we compared and analyzed LPS muscle parameters of GO patients before and after treatment in different treatment groups. It was found that the $T$ of LPS muscle showed significant decrease in different treatment effect groups. In the effective group, SIR of LPS muscle decreased after treatment both in T2WI-fs and T1WI-fs + C. Also, in the non-effective group, there was no significant change in SIR of LPS muscle. $T$ of LPS was also decreased in the non-effective group. This was consistent with the results of Xu et al.’s study.[23] Although edema and inflammation of LPS resolved and thickness decreased in the non-effective group, fibrotic complications of Müller’s muscle, LPS, and surrounding tissue adhesions were also present, resulting in persistent lid retraction. Therefore, compared to the $T$ of LPS muscle, SIR is more related to the therapeutic effect of subconjunctival triamcinolone acetone injection for GO patients with ptosis. Some studies also pointed out that Thyroid-Associated Ophthalmopathy (TAO) eyelid abnormalities cannot be simply qualitatively explained by thickening of LPS muscle. The degree and location of LPS muscle thickening and the impaired function of LPS muscle may be the key factors that determine the clinical manifestations of the eyelid.[14]

This study has the following limitations: 1) this study is essentially a retrospective study, therefore not all patients received orbital contrast-enhanced MR after treatment; 2) the number of cases is relatively small and single; and 3) lack of validation cases. Prospective studies with large sample size will be carried out in the future.

**Conclusion**

In GO patients with ULR as the main symptom, 3.0 T MRI could evaluate the therapeutic effect of triamcinolone acetone injection. Compared with the $T$ of LPS muscle, SI is a more sensitive indicator of the treatment effect. Moreover, the relative SI of LPS muscle on contrast-enhanced T1WI sequence before treatment has a better predictive value for treatment effect.

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**Conflicts of interest**

There are no conflicts of interest.

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