The Effect of Systemic Steroids and Orbital Radiation for Active Graves Orbitopathy on Postdecompression Extraocular Muscle Volume

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• PURPOSE: To evaluate the effect of orbital radiation prior to surgery on the clinical course and extraocular muscle (EOM) radiologic volume changes after decompression in Graves orbitopathy (GO).
• DESIGN: Retrospective, interventional case series.
• METHODS: The medical records of patients treated with orbital decompression for GO and who underwent postoperative orbital computed tomography were reviewed. Only patients who underwent rehabilitative decompression in the inactive phase and who received systemic corticosteroids alone (ST group) or combined orbital radiation and systemic corticosteroids (SRT group) in the active inflammatory phase of the disease were selected. The main outcome measure was the comparison of preoperative and postoperative EOM volumes. Secondary outcome measures were changes in proptosis and diplopia after decompression.
• RESULTS: Thirty-seven of 114 patients were selected for this study. There were no differences between the ST group (n = 22, 42 eyes) and SRT group (n = 15, 30 eyes) in terms of demographics or predecompression characteristics. After decompression surgery, the total EOM volume significantly increased by 15% in the ST group, but radiated EOMs in the SRT group did not expand, resulting in decreased induction of postoperative diplopia. The percentages of patients showing increased diplopia after decompression differed significantly between the groups (ST group, 40.9% vs SRT group, 13.3%, $P = .04$). However, there was no difference in exophthalmos reduction after decompression between the 2 groups.
• CONCLUSIONS: Orbital radiation prior to orbital decompression can reduce both the postoperative increase in EOM volume and deterioration in diplopia. (Am J Ophthalmol 2016;171:11–17. © 2016 Elsevier Inc. All rights reserved.)

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GRAVES ORBITOPATHY (GO) REFERS TO A PATHOLOGIC autoimmune condition characterized by lymphocytic infiltration and edema of the retrobulbar tissues, with potential thickening and fibrosis of the extraocular muscles (EOMs) and orbital fat.[1] It can lead to a discrepancy between the bony orbital cavity and the volume of the intraorbital soft tissue contents, resulting in disfiguring proptosis, motility disturbance, and optic neuropathy in GO patients.[2]

The mainstay therapy for GO in the active inflammatory phase is high-dose glucocorticoids and orbital radiotherapy (OR).[3] OR has been widely used to treat patients with active-phase GO for more than 70 years, and numerous previous retrospective and prospective studies have supported the efficacy of radiotherapy treatment for active GO.[4–7] In these previous studies, OR was well tolerated and effective in preventing exacerbations of active inflammation, in reducing soft tissue changes and proptosis, and especially in improving ocular motility impairment.[8–10] The main mechanism of OR is the anti-inflammatory effects caused by inducing apoptosis or disrupting the functions of radiosensitive lymphocytes and fibroblasts.[3,11]

Once the inflammation associated with GO becomes quiescent and a period of stability has been achieved, rehabilitative surgical therapy, such as orbital decompression, strabismus surgery, eyelid repositioning, and blepharoplasty, may be performed. Among these surgical treatments, orbital decompression is the primary treatment during the inactive or stable phase of the disease for correcting exophthalmos or exposure keratopathy, whereby the removal of portions of the bony orbit creates space for the enlarged orbital contents. However, some previous studies have reported EOM enlargement after orbital decompression; EOM enlargement may contribute to reducing the effect of orbital decompression, leading to the recurrence of orbital complications, such as proptosis, exposure keratitis, and compressive optic neuropathy.[12–14] Interestingly, we noted that EOM volume expansion after orbital decompression was less common in GO patients who underwent OR during the active phase than in those who did not undergo OR. Therefore, this study evaluated the effect of OR prior to surgery on the

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clinical course and postoperative EOM volume changes after decompression in GO patients.

METHODS

ALL PATIENTS WITH GO WHO UNDERWENT ORBITAL 2-WALL decompression by 1 surgeon (J.S.Y.) between January 2008 and December 2014 were retrospectively reviewed. The study protocol, which involved a retrospective chart review of all patients meeting the study criteria, was approved by the Institutional Review Board of the Severance Hospital of Yonsei University and adhered to the tenets of the Declaration of Helsinki. All patients provided their written informed consent.

Patients who underwent orbital decompression during the inactive phase and met all of the following criteria were included: (1) euthyroidism before the operation, (2) steroid pulse therapy with or without OR in the active phase, (3) chronic phase lasting longer than 6 months before the operation, (4) preoperative orbit computed tomography (CT) scans obtained within 2 months before the operation, and (5) postoperative orbit CT scans obtained at least 6 months after the operation. The ST group, which was the control group, only underwent steroid pulse therapy. Indications for corticosteroid treatment were: (1) periocular soft tissue inflammation (clinical activity score [CAS] 3 or greater), (2) compressive optic neuropathy, and (3) strabismus. In addition to concurrent or previous treatment with corticosteroids, the SRT group underwent OR. The primary indications for adding OR after intravenous (i.v.) corticosteroids were as follows: (1) continuation or even progression of inflammation despite i.v. steroid, (2) intolerance of corticosteroids, and (3) development of significant restriction of ocular motility. The exclusion criteria were concurrent periorbital diseases, thyroidectomy, or radioactive iodine-131 within 6 months before the operation; a history of EOM surgery; and orbital trauma.

The following parameters were compared to evaluate the matching of the 2 groups: (1) demographics (age and sex), (2) smoking history, (3) previous anti-thyroid treatment, (4) duration of the active and inactive phases of GO before decompression surgery, (5) activity as evaluated using the CAS,[15] (6) severity of GO at the time of surgery as evaluated by the modified NOSPECS,[16] (7) the subtype of GO as assessed using the Nunery type,[17] and (8) biochemical characteristics at the time of surgery.

The primary outcome measure was radiographic EOM volume changes between preoperative and postoperative CT scans (after orbital decompression). Secondary outcome measures were (1) changes in proptosis after decompression and (2) changes in diplopia as determined using the Gorman score.[18] The Gorman score is graded from 0 to 3 (0 = none, 1 = diplopia with gaze, 2 = intermittent diplopia, and 3 = constant diplopia).

In the active phase, all patients with a CAS of 3 or greater were treated with i.v. corticosteroids (500 mg methylprednisolone weekly for 6 weeks and 250 mg weekly for 6 weeks). Orbital radiation was targeted at the retrobulbar space at a dose of 20 Gy in 10 fractions over a 2-week period. Two-wall orbital decompression with posterior strut removal was performed in a chronic phase lasting longer than 6 months. The inferior orbital floor was exposed by the swinging eyelid approach, after lateral canthotomy, and the medial orbital wall was accessed via a transconjunctival approach. The bone and fat were removed incrementally, and the degree of residual proptosis was checked periodically by viewing the patient superiorly. The volume of fat removed during decompression surgery was measured using a 10-mL syringe.[19]

Data were analyzed using SPSS statistical software version 20.0 (SPSS Inc, Chicago, Illinois, USA). Independent *t* tests were used to compare ages, CAS values, NOSPECS scores, exophthalmos, the volume of removed fat during decompression surgery, and the time of postoperative CT scanning between the study groups. Sex, smoking history, Graves disease treatment, and percent of diplopia were compared between the study groups using Fisher exact tests. The Mann-Whitney test was used to compare the duration of the active and inactive phases before surgery between the 2 groups. Total EOM measurements were calculated as the sum of the measured medial rectus (MR), inferior rectus (IR), lateral rectus (LR), and superior rectus (SR) muscle volumes. The change in volume was calculated as the difference between the postoperative and preoperative volume measurements. Differences in preoperative and postoperative measurements were tested for significance using the paired *t* test.

RESULTS

A TOTAL OF 114 CLINICAL CHARTS OF PATIENTS WHO UNderwent orbital wall decompression were reviewed, and 37 patients (73 eyes) fulfilled the inclusion criteria. The ST group consisted of 22 patients (43 eyes) who were administered corticosteroids only, while the SRT group consisted of 15 patients (30 eyes) who underwent OR in addition to corticosteroid treatment. The average age at the time of the operation was 46.65 ± 10.51 years (range: 20–65 years), and 59% (22/37) of the patients were women. There were no differences in terms of age, sex, or smoking history between the SRT group and ST group (Table 1). Furthermore, the median duration of the active phase and the inactive phase before decompression surgery did not differ significantly between the 2 groups. There were no statistically significant differences in the maximal CAS value in the active phase, preoperative and postoperative CAS values, or modified NOSPECS scores between the 2 groups. In terms of subtype of GO, type 2 accounted

TABLE 1. Demographics of Patients With Graves Orbitopathy

	ST Group	SRT Group	*P*
Number of patients (eyes)	22 (42 eyes)	15 (30 eyes)	
Age (range), y, mean ± SD	44.32 ± 9.09 (31–60)	50.07 ± 11.79 (20–65)	.103[a]
Female sex, % (n)	64% (14)	53% (8)	.734[b]
Smoking history, % (n) (current/ex/never)	9/36/55 (2/8/12)	13/33/53 (2/5/8)	1.000[b]
Treatment of Graves disease, % (n) (ATD/RAI/surgery)	82/9/9 (18/2/2)	80/7/13 (10/3/2)	.543[b]
Duration of active phase, median (IQR)	7 (5–11)	8 (6–15)	.213[c]
Duration of inactive phase before decompression, median (IQR)	10.5 (6.75–18.5)	7 (6–14)	.262[c]
CAS			
Max in active phase	3.93 ± 0.91	4.33 ± 1.03	.082[a]
Preoperative	0.60 ± 0.73	0.47 ± 0.51	.373[a]
Postoperative	0.53 ± 0.63	0.50 ± 0.57	.625[a]
Modified NOSPECS score	5.81 ± 1.20	6.23 ± 1.84	.308[a]
Subtype of GO, type 1:2, n (%)	7:15 (31.8:68.2)	2:13 (13.3:86.7)	.262[b]
Total T3 (0.58–1.59 ng/mL), mean ± SD	1.31 ± 0.91	1.24 ± 0.42	.332[a]
fT4 (0.70–1.48 ng/dL), mean ± SD	1.25 ± 0.62	1.44 ± 0.53	.459[a]
TSH (0.35–4.94 μIU/mL), mean ± SD	1.25 ± 2.05	0.90 ± 1.29	.645[a]
M22-TRAb (≤1.75 IU/L), mean ± SD (positive %)	9.2 ± 12.72 (81.8%)	9.5 ± 9.36 (80%)	.957[a]
Mc4-TSI (≥140 SRR%), mean ± SD (positive %)	323.44 ± 118.89 (81.8%)	365.83 ± 99.28 (86.7%)	.647[a]

ATD = antithyroid drug; CAS = clinical activity score; GO = Graves orbitopathy; IQR = interquartile range; RAI = radioiodine therapy; SD = standard deviation; SRR = specimen-to-reference ratio; SRT = combination of steroid and radiotherapy; ST = steroid only; TSH = thyroid-stimulating hormone; TRAb = TSH receptor antibody; TSI = thyroid-stimulating immunoglobulin.

[a]Independent *t* test.

[b]Fisher exact test.

[c]Mann-Whitney test.

for 68.2% (15/22) in the ST group and 86.7% (13/15) in the SRT group; these percentages were not significantly different ($P = .262$). Comparison of peripheral thyroid function test results and thyroid-stimulating hormone receptor autoantibody findings also yielded no statistically significant differences. Four patients were diagnosed with compressive optic neuropathy in the active phase; 2 of these patients were included in the SRT group and the other 2 patients were included in the ST group. All 4 of these patients showed regression of optic neuropathy after both treatments and there was no recurrence of optic neuropathy during the follow-up period.

The mean reduction in exophthalmos after decompression surgery was not statistically significantly different ($P = .320$, Table 2). However, patients with increased diplopia after decompression surgery, as evaluated using the Gorman score, comprised 40.9% of the ST group and 13.3% of the SRT group; there was a statistically significant difference between the 2 groups ($P = .040$).

There was no significant difference in the preoperative volume of the rectus muscle between the SRT group and the ST group ($P = .230$ total, $P = .067$ LR, $P = .054$ IR, $P = .236$ MR, and $P = .476$ SR). As shown in Table 3, the total EOM volume increased by an average of 15% from a mean preoperative volume of 4.62 ± 2.07 mL to a mean postoperative volume of 5.29 ± 2.55 mL in the ST group ($P < .001$). All rectus muscles in the ST group showed significant increases in volume, and the MR and IR, in particular, showed marked enlargement. However, there was no significant volume change in any rectus muscle in the SRT group postoperatively ($P = .291$ total, $P = .077$ LR, $P = .571$ IR, $P = .523$ MR, and $P = .494$ SR). There was no significant correlation between the change in proptosis (mm) or the change in total EOM volume (mL) after decompression surgery ($r = -0.302$, $P = .052$ in the ST group; $r = -0.068$, $P = .722$ in the SRT group). The mean volume of fat removed during decompression surgery was 3.69 ± 1.23 mL in the ST group and 3.93 ± 1.15 mL in the SRT group, which was not significantly different ($P = .447$) (Supplemental Table, available at AJO.com).

On average, postoperative CT scans were obtained 11.7 months (range: 6–19 months) after surgery. There was no statistically significant difference in the duration to postoperative CT scanning between the 2 groups

TABLE 2. Clinical Outcome of Orbital Decompression in Two Groups

	ST Group (N = 22, 42 Eyes)	SRT Group (N = 15, 30 Eyes)	*P*
Exophthalmometry, mean ± SD, mm			
Preoperative	20.69 ± 2.39	20.33 ± 2.37	.535[a]
Postoperative	16.28 ± 2.32	15.47 ± 2.11	.131[a]
Exophthalmos reduction	4.40 ± 1.46	4.80 ± 1.30	.320[a]
Diplopia evaluated using a Gorman score (0:1:2:3)			
Preoperative, n (%)	7:10:2:3 (31.8/45.5/9.1/13.6)	2:6:3:4 (13.3/40.0/20.0/26.7)	.468[b]
Postoperative, n (%)	3:9:5:5 (13.6/40.9/22.7/22.7)	1:6:4:4 (6.7/40.0/26.7/26.7)	1.00[b]
Increased, % (n)	50.0 (11)	13.3 (2)	.035*[b]

SRT = combination of steroid and radiotherapy; ST = steroid only.
Asterisk denotes statistical significance, $P < .05$.
[a]Independent *t* test.
[b]Fisher exact test.

TABLE 3. Preoperative and Postoperative Volume of Extraocular Muscles Following Orbital Decompression in Two Groups

	ST Group (42 Eyes)				SRT Group (30 Eyes)			
	Preoperative Volume (mL)	Postoperative Volume (mL)	Change in Volume (mL)	*P*[a]	Preoperative Volume (mL)	Postoperative Volume (mL)	Change in Volume (mL)	*P*[a]
Total	4.62 ± 2.07	5.29 ± 2.55	0.68 ± 0.90	<.001*	5.30 ± 2.26	5.83 ± 3.21	−0.53 ± 2.69	.291
LR	0.88 ± 0.55	1.05 ± 0.67	0.17 ± 0.44	.019*	1.16 ± 0.55	1.00 ± 0.67	−0.15 ± 0.46	.077
IR	1.35 ± 0.72	1.62 ± 0.92	0.27 ± 0.62	.007*	1.70 ± 0.78	1.63 ± 0.81	−0.08 ± 0.66	.571
MR	1.26 ± 0.83	1.54 ± 0.95	0.28 ± 0.59	.004*	1.53 ± 0.81	1.61 ± 0.75	0.09 ± 0.66	.523
SR	0.87 ± 0.71	1.01 ± 0.73	0.14 ± 0.41	.031*	0.99 ± 0.72	0.96 ± 0.80	−0.04 ± 0.30	.494

IR = inferior rectus muscle; LR = lateral rectus muscle; MR = medial rectus muscle; SR = superior rectus muscle; SRT = combination of steroid and radiotherapy; ST = steroid only; Total = sum of all rectus muscle volumes.
Asterisk denotes statistical significance, $P < .05$.
[a]Paired *t* test.

(12.1 months in the ST group vs 11.1 months in the SRT group, $P = .507$).

The Figure shows a representative case demonstrating differences in postoperative volumetric changes of the EOMs between a radiated orbit and a nonradiated orbit. This patient showed asymmetric active inflammation and received combined systemic steroids and unilateral orbital radiation at the left orbit, after which he underwent bilateral decompression in the inactive phase. Interestingly, after surgery, the EOM volume was increased in the nonradiated orbit, but not in the radiated orbit, on postoperative CT.

DISCUSSION

THIS STUDY SHOWED THAT OR PRIOR TO ORBITAL DECOMpression could reduce the postoperative increase in EOM volume as well as the deterioration of diplopia. However, OR had no effect on postoperative changes in proptosis.

Consistent with previous studies, the postoperative volume increased in the total EOMs of the nonradiated orbit by an average of 15% in this study. In a study by Alsuhaibani and associates, a significant increase of 16.5% in the volume of the MR muscle was detected, and a greater increase in postoperative MR muscle volume was associated with a smaller reduction in proptosis after surgery.[12] Hue and associates also reported that the MR muscle significantly increased (by 27%) from its preoperative volume in orbits that underwent orbital decompression.[14] Similarly, progressive enlargement of the EOMs after orbital decompression was detected in 3 patients who presented with recurrent compressive optic neuropathy in a study by Wenz and associates.[13]

The exact reason for the postoperative volumetric increase in the EOMs is not clear. Hu and associates hypothesized that the postoperative volumetric increase in the

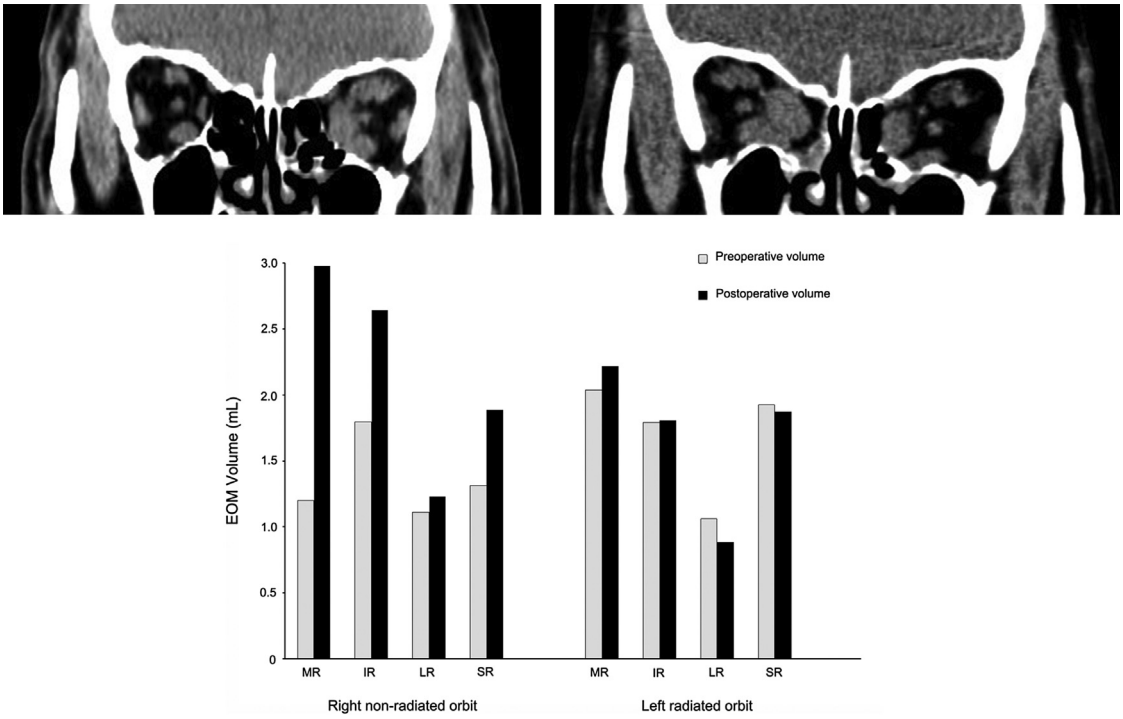

FIGURE. Representative case showing the effect of previous orbital radiation on the outcome of rehabilitative decompression. (Top left) A preoperative coronal computed tomography scan of a patient with inactive Graves orbitopathy documenting unilateral marked extraocular muscle enlargement in the left orbit is shown. He was treated with combined steroid pulse therapy and unilateral radiotherapy on the left orbit in the active phase. (Top right) A postoperative coronal computed tomography scan of the same patient who underwent bilateral 2-wall orbital decompression is shown. In the right nonradiated orbit, significant increases in the volumes of the medial rectus and inferior rectus are observed as compared with those on preoperative computed tomography. No extraocular muscle enlargement was observed after decompression in the left radiated orbit. (Bottom) Preoperative and postoperative extraocular muscle values in the right non-radiated orbit, as compared with the left radiated orbit, are shown.

EOMs observed after orbital decompression may be attributable to a mild inflammatory reaction that may occur after surgery and hydrostatic pressure changes that occur because of the expanded orbital volume created by the surgery.[14] Moreover, another possible cause may be venous stasis owing to postoperative movement of the EOM belly into the sinus cavity at an acute angle near the orbital apex that may lead to muscular blood flow impairment.[12,20]

In contrast to EOMs in nonradiated orbits, EOMs in radiated orbits were not found to expand in the present study. Possible explanations for the effect of OR on EOM volume after decompression are increased stiffness caused by radiation fibrosis, a decrease in venous stasis in the orbital tissue owing to shrinkage of the local blood vessels, or a combination of these 2 factors. Fibrosis is one of the most common pathologic changes produced by OR.[21] According to classic theories of radiation effects, radiation induces double-strand breaks in DNA as an early response and causes slowed proliferation rates, apoptosis, and radiation fibrosis as a late response.[22] Radiation fibrosis may increase stiffness in the EOMs and orbital connective tissues (eg, fat, the intermuscular septum, muscle capsule, and muscle pulley sleeve). It may reduce the distensibility and plasticity of the orbital tissues; consequently, postoperative EOM enlargement in GO patients with OR can be lessened.[23] Blood vessel changes induced by radiation may also be involved. Radiation leads to a shrinkage of local blood vessels in orbital tissue owing to a combination of perivascular fibrosis, direct damage to the vascular wall, and occlusion of the vasa vasorum.[24] For this reason, the blood supply to the orbital tissue is reduced, which may prevent massive perioperative bleeding, muscle edema owing to venous stasis, and postoperative subclinical inflammation induced by an intravascular inflammatory mediator.[25]

In consideration of postoperative clinical implications of prior OR for GO patients, marked EOM enlargement could minimize the effect of orbital decompression, allowing the globe to recede, and OR may enhance the effect of a reduction in proptosis by preventing postoperative EOM enlargement.[12] Similarly, in a multivariate analysis of risk factors and outcomes of thyroid-related orbital decompression surgery, Wu and associates reported that OR was an independent predictor of a greater reduction in proptosis.[26] They suggested that, as OR has been shown to cause a

modest improvement in extraocular motility impairment, it may also lessen extraocular muscle swelling after decompression surgery, and thereby lead to more marked proptosis reduction. This explanation is in agreement with the result of postoperative EOM volume changes noted in the present study. On the other hand, Baldeschi and associates reported that the total radiation dose, fraction size, and irradiated volume commonly used to treat active GO did not adversely affect the outcome of rehabilitative decompression surgery.[27] In a comparison among groups that underwent OR alone, systemic glucocorticoid treatment alone, or both OR and glucocorticoid treatment, there were no differences in surgical outcomes, including the reduction in proptosis, lid retraction, and diplopia. We have shown a similar result, in that there was no significant beneficial effect on proptosis. We showed a similar level of proptosis reduction in the 2 groups, who had similar bony volume expansion and fat removal, although only the ST group showed increased EOM volume after decompression. This finding may be attributable to multiple anatomic individual factors that influence tissue prolapse into the decompressed bone, such as a combination of the amount of bone removed, the resilience of the orbital tissue, the adhesion between the adjacent tissue plane and intraorbital or retroorbital pressure, and the volume of EOM enlargement.[23,28]

Patients with OR were shown to have a lower rate of diplopia deterioration (13.3%) after decompression surgery than the steroid-only group. Postoperative diplopia after a 2-wall decompression is caused by the expansion and displacement of EOMs and orbital connective tissue into the adjacent sinuses; the incidence of worsened EOM imbalance after orbital decompression has previously been reported to be 27%–80%.[29,30] In patients who underwent OR prior to decompression in the present study, the reduced postoperative EOM enlargement may have led to less severe EOM restriction and imbalance.[31]

The limitations of this study included its retrospective study design, which may have led to subject selection bias, and the relatively small number of included patients. Although the preoperative clinical features were not significantly different between the 2 groups, the SRT group may have included more patients with progressive disease, despite i.v. steroid treatment, having more fibrotic extraocular muscles that respond differently to decompression, with less expansion. Albeit not statistically significant, there were more type 2 patients with motility defects in the SRT than in the ST group. Despite these shortcomings, this report represents the clinical implications of prior OR on the outcome of rehabilitative decompression in GO patients.

In this study, prior OR treatment could reduce diplopia deterioration after orbital decompression by preventing postoperative EOM enlargement. Our results suggest that OR should be considered as a treatment for GO patients showing active inflammatory myopathy, particularly before undergoing orbital decompression.

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