• Clinical Research •

The effect of intravenous high-dose glucocorticoids and orbital decompression surgery on sight-threatening thyroid-associated ophthalmopathy

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Abstract

• AIM: To report the effects of intravenous high-dose glucocorticoids (ivGC) and orbital decompression (OD) surgery for treatment of sight-threatening thyroid-associated ophthalmopathy (TAO).

• METHODS: A retrospective review of medical records from patients with sight-threatening TAO [definite or highly suspected dysthyroid optic neuropathy (DON)] treated with ivGC (60 cases) and OD (25 cases) was conducted at the Zhongshan Ophthalmic Center between January 2001 and January 2009. Patients were initially treated with ivGC (ivGC group). If no significant improvement in visual function was obtained, they then received OD surgery (OD group). The pre- versus post-treatment efficacies of either ivGC or OD in these patients were assessed using several indices, including visual acuity, intraocular pressure, ocular alignment, ocular motility, and exophthalmos.

• RESULTS: Nighty-one eyes had definite DON while 79 were considered to have highly suspected DON. In the ivGC group, 51 individuals (85.0%) eventually demonstrated normal vision, while 10 patients (16.7%) demonstrated a reduction in deviation (P<0.01), and 35 cases (58.3%) showed slight improvements in ocular motility (P<0.01). In OD group, visual acuity improved in 24 cases (96.0%, P<0.01) and all patients showed varying reductions of exophthalmos (mean: 4.35±1.13 mm, P<0.01). Eight cases (32.0%) experienced an 8-15 PD reduction of deviation and ocular motility improved in 12 cases (48.0%), while 3 patients (12.0%) developed new-onset strabismus with diplopia post-surgically (P<0.01). Patients were followed up at an average of 1.55±1.07y.

• CONCLUSION: Both ivGC and OD show good therapeutic efficacy in the treatment of sight-threatening TAO. The presence of extremely poor eyesight (≥0.5logMAR) was corrected in some patients with ivGC alone, thus sparing these patients from subsequent OD surgery. In patients who were refractory to steroids, subsequent OD surgery often provided satisfactory outcomes, however, new-onset strabismus with diplopia was observed in 12.0% of these cases.

• KEYWORDS: thyroid-associated ophthalmopathy; dysthyroid optic neuropathy; glucocorticoids; orbital decompression; orbital surgery

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INTRODUCTION

Thyroid-associated ophthalmopathy (TAO) or thyroid orbitopathy is the most common cause of unilateral or bilateral proptosis, accounting for approximately 39.3%-42.2% of all orbital diseases in adults[1]. The majority of patients present with mild thyroid orbitopathy, characterized by variable lid swelling, lid retraction, and mild exophthalmos. These patients experience minimal photophobia, tearing, ocular fatigue and other ocular discomforts. In these cases, regular follow-up counseling and local preservative-free artificial tears are recommended. In contrast to these mild cases, about 5%-6% of these patients progress to develop severe orbitopathy[2], which results in sight-threatening features including exophthalmos along with significant soft tissue features and myopathy, exposure keratitis and even optic neuropathy. Although small proportion of TAO patients are likely to deteriorate as sight-threatening cases, once that happens, this disease could seriously impact patient's quality of life[3-4].

Dysthyroid optic neuropathy (DON) is a condition that compression of the orbital apex leads to impairment of visual function[5-6]. It is usually treated with high-dose of glucocorticoids or orbital decompression (OD). Glucocorticoid pulse therapy can reduce inflammation, while OD spares

space for optic nerve and relieve the pressure around it[7]. The EUGOGO recommendation for patients with DON includes high-dose intravenous corticosteroids (ivGC) combined with a subsequent application of OD if there is little or no response to corticosteroids[8]. However, published data are very rare for each treatment strategy. Therefore, managing patients with DON remains a challenge for many clinicians, and protocols for this condition continue to evolve.

In this study, we reviewed the case records of previously untreated patients with definite or highly suspected DON who were treated with ivGC and OD in a tertiary referral hospital in China over the past 10y. From this review we found that ivGC, by itself, was very effective in correcting extremely poor eyesight, more than 0.5 logMAR in Logarithmic Early Treatment Diabetic Retinopathy Study (ETDRS) Visual Acuity Chart, in some patients, thus sparing them from surgical treatment. In patients who were refractory to steroids, OD often provided a satisfactory outcome (mainly visual acuity improve by more than 2 lines). In some patients, who experienced vision loss after successful OD, their vision was restored following ivGC treatment.

SUBJECTS AND METHODS

Ethical Approval This retrospective study was performed in compliance with the Declaration of Helsinki, and approved by the ethics committee of the Zhongshan Ophthalmic Center. Informed consent was obtained from the subjects.

Patients A retrospective analysis of medical records was conducted for cases with severe TAO as treated by a single ophthalmologist (Yan JH) at the Zhongshan Ophthalmic Center of Sun Yat-sen University between January 2001 and January 2009.

Definite DON cases refer to those with optic disc swelling, impairment of color vision, together with radiological evidence of apical optic nerve compression. If optic disc swelling was not present or could not be observed because of opaque refractive media, highly suspected DON was diagnosed by the following two or more signs combined: abnormal color vision, an increased latency showed in visual evoked potential (VEP), visual field loss compatible with optic nerve stretch or apical muscle crowding showed in radiological images, and presence of a relative afferent pupillary defect (RAPD). Exclusion criteria were: 1) previous orbital radiation therapy; 2) treated by ivGC or OD before; 4) failed to cooperate with follow-up investigations.

Comprehensive ophthalmological assessments were performed before therapy and at the follow-up period. For each subject, the following data were recorded before treatments: 1) basic information and medical history including gender, age, duration of thyroid disease, previous treatment for thyroid disease, family history, ophthalmological history and smoking habits; 2) best corrected visual acuity, intraocular pressure (IOP), orbital pressure, slit-lamp examination of the anterior segments, pupil examination, fundus examination, eyelid swelling, eyelid retraction, von Graefe's sign, lagophthalmus, conjunctival hyperemia, swelling of the caruncle, ocular alignment and motility. Proptosis was assessed by Hertel exophthalmometry. In addition, a major synoptophore examination and prism cover test were included within our routine examinations for evaluating the exact eye deviation and binocular vision. Color vision test (FM 100-hue test), VEP and automated perimetry were performed to enable a comprehensive and detailed assessment of each case. Diplopia was detected using red filter test. Patients were asked to answer no diplopia, intermittent diplopia, or constant diplopia in any gazing directions. Orbital magnetic resonance imaging (MRI) or computed tomography (CT) was performed on all patients. The severity and activity of TAO were evaluated using the NOSPECS, European Group on Graves Ophthalmopathy (EUGOGO) and Clinical Activity Score (CAS) criteria, respectively. In the follow-up, best corrected visual acuity, IOP, slit-lamp examination of the anterior segments, fundus examination, proptosis assessment, eye deviation, ocular movement, and CAS score of each patient were recorded.

Principle of Treatment Our steroid pulse therapy was based on those of van Geest *et al*[9] and Higashiyama *et al*[10]. Before receiving treatment, all the patients were required to undergo a general physical examination including routine blood and urine assays, blood biochemistry, liver and kidney function tests, blood clotting index tests, electrocardiographic examination, chest X-ray and thyroid function examination. Initially, an intravenous high dose of steroids (0.5 or 1 g methyl prednisolone per day) was administered for 3d, followed by oral prednisone. If their visual function gradually recovered, a subsequent OD was considered unnecessary. If response was poor or even absent after 2 courses of ivGC, specifically 1) severe corneal exposure occurred, or 2) visual acuity improve no more than 2 lines, or 3) IOP stay high as ≥21 mm Hg, or 4) optic disc swelling still existed, then they would receive OD. Therefore, our patients were divided into two groups, the ivGC group (who received ivGC alone) and the OD group (who received ivGC followed by OD). Patients were followed-up for an average of 1.55±1.07y (range 1-8y). All steroid-related side effects (Cushingoid appearance, hypertension, diabetes, gastric irritation and osteoporosis) and surgical-related complications (orbital hemorrhage, sinusitis, cerebrospinal fluid leakage, infraorbital hypoesthesia, lower lid entropion and newly-developed strabismus) were recorded in detail.

Intravenous High-dose Glucocorticoids Therapy The schedule for ivGC therapy initially involved a daily dose of 0.5 g or 1.0 g methylprednisolone for 3d, followed by a daily

dose of 40-60 mg oral prednisone for the following 4d. When the patient' age was more than 65 years old or their body weight was less than 50 kg, we chose a daily dose of 0.5 g methylprednisone, otherwise we used a daily dose of 1.0 g methylprednisone. Patients often received 1-3 such courses of treatment (an average of 1.82±0.62 courses) with 61.7% receiving 2 courses of treatment. Additional drugs for protecting gastrointestinal mucous membrane, potassium and calcium supplements, and sedatives were used as required. In the ivGC group, the average cumulative dose of methylprednisolone was 4.89±1.92 g, with an average daily infusion of 0.74±0.25 g. Patients with contraindications for ivGC (hypertension, diabetes, tuberculosis and gastrointestinal ulcer) were excluded.

Orbital Decompression Surgery When no significant improvements in visual function, for example, less than 2 lines in visual acuity, were obtained after administration of ivGC therapy (after 2 courses), patients received OD while under general anesthesia. We waited for one week after the last steroid dose and move the patient from the ivGC group to the surgical decompression. Our commonly used surgical techniques consisted of decompression of the deep lateral wall, both medial and inferior walls, balanced removal of the medial and deep lateral walls and uniting the inferomedial with the lateral wall. In all cases, adipose tissue removal was performed. Post-operative steroid therapy consisted of intravenous injections of 10-15 mg/d dexamethasone or 60-80 mg/d methylprednisolone for 3-5d, followed by oral prednisone at 40-60 mg/d, which was then reduced by 5 mg per week over the following 8-12wk.

Statistical Analysis Statistical analysis was performed to assess pre- versus postoperative results within these two groups as achieved with use of paired samples *t*-tests for continuous variables such as IOP and degree of exophthalmos. The Mann-Whitney *U* test or the Wilcoxon rank sum test was used for an abnormal distribution or zero values. χ^2 test was used for categorical data. The SPSS software version 24.0 (SPSS, Chicago, IL, USA) was used for all statistical analyses. $P<0.01$ was required for results to be considered statistically significant.

RESULTS

Population Characteristics Between January 2001 and January 2009, 142 severe TAO cases were included in our study. Finally, 85 patients were brought into our analysis with relatively completed medical records and matched the standard of diagnosis mentioned above. Their clinical characteristics of are summarized in Table 1. Female (32 patients) account for 37.6% of the population, while male represented the majority of 62.4%. At that time, 28 admitted that they were current smokers, including 26 males and 2 females. Graves' disease was the predominant thyroid disease, which occupied 90.6% of the whole. Before the referral, more than half of our patients (60.0%) were treated with antithyroid drugs in the local hospital. The number came with 37.6% of the patients who undergone thyroidectomy. Only two of our subjects received radioiodine treatment. We have confirmed that our patients' euthyroidism had all restored and stably maintained before we plan for their ophthalmic therapy.

Table 1 Clinical characteristics of the subjects *n* (%)

Parameters	Number of the subjects
Gender (F/M)	32/53
Smoking habits	
Never smoked	51 (28 females, 23 males)
Past smokers	6 (2 females, 4 males)
Current smokers	28 (2 females, 26 males)
Thyroid diseases	
Graves' disease	77 (90.6)
Hashimoto thyroiditis	8 (9.4)
Treatment for thyroid diseases before visit us	
Antithyroid drug	51 (60.0)
Total thyroidectomy	32 (37.6)
Radioiodine treatment	2 (2.4)
Age (median)	
On diagnosis of thyroid disease	51y
At onset of eye symptoms	52y
On diagnosis of severe TAO	55y

TAO: Thyroid-associated ophthalmopathy.

Table 2 Clinical features of eyes with definite and highly suspected DON *n* (%)

Parameters	Definite DON	Highly suspected DON
Number of eyes	91	79
Impairment of color vision	91 (100)	18 (22.8)
Visual field defects	65 (71.4)	48 (60.8)
Abnormal VEP latency	68 (74.7)	63 (79.7)
RAPD	21 (23.1)	13 (16.5)
In ivGC group	67	53
In OD group	24	26

DON: Dysthyroid optic neuropathy; VEP: Visual evoked potential; RAPD: Relative afferent pupillary defect; ivGC: High-dose intravenous corticosteroids; OD: Orbital decompression.

Clinical Features of Definite DON and Highly Suspected DON Sixty-four patients (75.3%) were diagnosed with definite DON, including 91 affected eyes. Seventy-night eyes were considered to have highly suspected DON. In ivGC group, there are 16 subjects diagnosed with bilateral definite DON and 9 patients with highly suspected features in both eyes. In OD group, 11 patients were considered to have bilateral definite DON. Clinical features of eyes with definite and highly suspected DON are demonstrated in Table 2.

High-dose Intravenous Corticosteroids Results

General data A total of 60 cases (40 males and 20 females) comprised the ivGC group, with mean age of 49.67±13.83y (range: 19-82y). Primary ailments experienced by this group included decreased visual acuity (81.7%), exophthalmos (86.7%), restricted ocular motility (81.7%), double vision (76.7%), eye redness, swelling and pain (66.7%) and squint (43.3%). In 7 cases (14 eyes) with normal visual acuity (20/20) in both eyes, visual functional tests (pupil examination, color vision, or VEP) showed obvious abnormalities. All cases were classified as active TAO (CAS score ≥3). By EUGOGO assessment, 3 cases (5.0%) were considered as moderate-to-severe TAO and 57 cases (95.0%) as sight-threatening TAO. On the basis of NOSPECS classification, 2 cases (3.3%) were classified as Grade 5 (corneal involvement) and 58 cases (96.7%) were Grade 6 (sight loss). The relevant data of patients in both groups are shown in Table 3.

Final follow-up results Patients were followed-up at an average of 1.23±0.43y (range: 1-2y). All the patients became inactive after steroid therapy.

Visual acuity and intraocular pressure Fifty-one patients (85.0%) demonstrated normal visual acuity (20/20) in both eyes at final follow-up. Thirty-eight patients (63.3%) showed improved vision in both eyes for more than 2 lines (P<0.01), 23 eyes (19.2%) experienced either slight vision improvement or remained the same and a mild decrease in vision was observed in 2 cases (3.3%). The IOP was normal in 59 cases (98.3%) and only 1 case showed a mild increase in IOP (23 mm Hg, by non-contact tonometer) within the left eye (P<0.01).

Exophthalmos reduction There were no obvious changes of exophthalmos in 35 cases (58.0%), while 42 eyes (35.0%) showed a mean reduction of 1.78±0.67 mm proptosis (P<0.01).

Improvements in diplopia Twelve patients (20.0%) mentioned that the treatment provided relief from double vision. In general, significant improvements were shown in ocular alignment and ocular motility. Ten cases (16.7%) demonstrated a reduced deviation of 8-15 PD (P<0.01). Slight improvements in ocular motility were seen in 35 cases (58.3%), with 5 cases (8.3%) showing improvements of 75% in the direction of the previously restricted area and the remaining cases improved 25%-50% in the previously restricted direction (P<0.01).

Complications Eight patients (13.3%) demonstrated a mild disorder of glycometabolism, with no diabetes. During the course of drug treatment, 14 individuals (23.3%) experienced digestive symptoms and 19 patients (31.7%) showed a slight appearance of Cushing's. No serious complications such as hypokalemia, liver or kidney damage, depression, osteoporosis, infection and blood hypertension were observed. Parameters before and after treatment of the patients in both groups are shown in Table 4.

Table 3 Baseline findings in both ivGC group and OD group *n* (%)

Parameters	IvGC group	OD group
Number of patients (eyes)	60 (120)	25 (50)
Age[a] (range), y	49.67±13.83 (19-82)	49.16±8.24 (31-63)
Gender[a]		
Male	40 (67.7)	13 (52.0)
Female	20 (33.3)	12 (48.0)
Visual acuity[b], logMAR		
≤0.1	22 (18.3)	1 (2.0)
>0.1-0.3	56 (46.7)	17 (34.0)
>0.3-0.5	16 (13.3)	12 (24.0)
>0.5-1.0	14 (11.7)	7 (14.0)
>1.0	4 (3.3)	2 (4.0)
FC	6 (5.0)	9 (18.0)
HM	2 (1.7)	2 (4.0)
IOP[b] (mm Hg)	21.37±5.93	19.45±6.11
11-21	76 (63.3)	36 (72.0)
>21	44 (36.7)	14 (28.0)
Pupil examination[b]		
Pupil size		
Normal	29 (24.2)	11 (22.0)
Dilated	79 (65.8)	33 (66.0)
Pupillary light reflex		
Brisk	8 (6.7)	2 (4.0)
Sluggish	87 (72.5)	38 (76.0)
Nonreactive	13 (10.8)	4 (8.0)
Unavailable data	12 (10.0)	6 (12.0)
Color vision[b] (FM 100-hue test)		
Normal	25 (20.8)	6 (12.0)
Mild decline in blue-green hues	43 (35.9)	19 (38.0)
Obvious abnormality	36 (30.0)	11 (22.0)
Unavailable data	16 (13.3)	14 (28.0)
Visual field test[b]		
Normal	18 (15.0)	1 (2.0)
Defect	76 (63.3)	37 (74.0)
Peripheral & partial	21 (17.5)	11 (22.0)
Peripheral & wide	23 (19.2)	7 (14.0)
Central visual field related	32 (26.7)	19 (38.0)
Unavailable data	26 (21.7)	12 (24.0)
Visual evoked potential[b] (P100)		
Normal	8 (6.7)	0
Mildly abnormal	37 (30.8)	7 (14.0)
Severe abnormal	75 (62.5)	43 (86.0)
NOSPECS[a] (grade)		
Corneal involvement (Grade 5)	2 (3.3)	2 (8.0)
Sight loss (Grade 6)	58 (96.7)	23 (92.0)
EUGOGO[a] (grade)		
Moderate-to-severe	3 (5.0)	1 (4.0)
Sight-threatening	57 (95.0)	24 (96.0)
CAS score[a]		
Inactive GO (CAS<3)	0	2 (8.0)
Active GO (CAS≥3)	60 (100)	23 (92.0)
Follow-up period (range), y	1.23±0.43 (1-2)	2.32±1.65 (1-8)

OD: Orbital decompression; FC: Finger counting; HM: Hand motion; IOP: Intraocular pressure; GO: Graves' ophthalmopathy. [a]Number of patients; [b]Number of eyes.

Table 4 Clinical parameters before and after treatment *n* (%)

Parameters	IvGC group		*P*	OD group		*P*
	Before treatment	After treatment		Before treatment	After treatment	
CAS score[a]	7	2	<0.01[d]	6	2	<0.01[d]
Inactive GO (CAS<3)	0	60 (100)		2 (8.0)	25 (100)	
Active GO (CAS≥3)	60 (100)	0		23 (92.0)	0	
Decrease	60 (100)			23 (92.0)		
No change	0			2 (8.0)		
Visual acuity, logMAR[b]			<0.01[d]			<0.01[d]
Improve≥2 lines	95 (79.2)			26 (52.0)		
No change<2 lines	23 (19.2)			22 (44.0)		
Deteriorate≥2 lines	2 (1.6)			2 (4.0)		
≤0.1	104 (86.7)			18 (36.0)		
>0.1-0.3	9 (7.5)			14 (28.0)		
>0.3-0.5	5 (4.2)			8 (16.0)		
>0.5-1.0	1 (0.8)			5 (10.0)		
>1.0	1 (0.8)			4 (8.0)		
FC	0			1 (2.0)		
HM	0			0		
IOP (mm Hg)[b]	21.37±5.93	15.59±2.14	<0.01[c]	19.45±6.11	15.63±2.21	<0.01[c]
Proptosis (mm)[b]	21.13±2.66	20.50±2.72	<0.01[c]	22.61±1.23	18.26±1.10	<0.01[c]
Decrease≥2	27 (22.5)			50 (100)		
No change<2	93 (77.5)			0		
Diplopia[a]						
Pre-existing	46 (76.7)			19 (76.0)		
Improve	12 (20.0)			8 (32.0)		
No change	32 (53.3)			9 (36.0)		
Deteriorate	2 (3.3)			2 (8.0)		
New-onset	0			3 (12.0)		
Complications[a]						
Disorder of glycometabolism	8 (13.3)			2 (8.0)		
Digestive symptoms	14 (23.3)			2 (8.0)		
Appearance of Cushing's	19 (31.7)			3 (12.0)		
Upper eyelid retraction	0			2 (8.0)		
New-developed strabismus	0			3 (12.0)		

OD: Orbital decompression; FC: Finger counting; HM: Hand motion; IOP: Intraocular pressure; GO: Graves' ophthalmopathy. [a]Number of patients; [b]Number of eyes; [c]Paired-samples *t*-test; [d]Wilcoxon rank sum test. *P*<0.01 was required for results to be considered statistically significant.

Orbital Decompression Results

General data A total of 25 cases (13 males and 12 females) comprised the OD group, with mean age of 49.16±8.24y (range: 31-63y). Primary ailments included decreased visual acuity (98.0%), exophthalmos (92.0%), restricted motility (80.0%), double vision (76.0%) and squint (40.0%). Visual functional tests of all the patients showed obvious abnormalities. Twenty-three cases (92.0%) were evaluated as active TAO (CAS score ≥3) and 2 patients (8.0%) as inactive TAO with CAS scores of <3. By EUGOGO assessment, one case (4.0%) was classified as moderate-to-severe TAO and 24 cases (96.0%) as sight-threatening TAO. According to NOSPECS classification, 2 cases (8.0%) were classified as Grade 5 (corneal involvement) and 23 individuals (92.0%) as Grade 6 (sight loss). A decompression of deep lateral and inferior orbital walls were performed in 2 eyes (4.0%), balancing of deep lateral and medial orbital walls in 4 eyes (8.0%), medial and inferior orbital walls in 22 eyes (44.0%) and deep lateral orbital wall united with medial and inferior orbital walls in 22 eyes (44.0%).

Final follow-up results Patients were followed-up at an average of 2.32±1.65y (range: 1-8y). All 25 patients became inactive TAO at final follow-up.

Visual acuity and intraocular pressure Visual acuity

improved in 24 patients (47 eyes, 94.0%) as assessed at final follow-up. The average increase was 2.70±2.22 lines and 26 eyes (52.0%) increased their eyesight by more than 2 lines (P<0.01). However, the visual acuity decreased by 2 lines in 1 patient. All the patients showed normal IOP after surgeries (P<0.01).

Exophthalmos reduction All patients showed varying reductions of exophthalmos (range: 3-7 mm, mean: 4.35±1.13 mm) after OD (P<0.01). A maximal reduction of 7 mm exophthalmos within both eyes was obtained in 1 patient (4.0%) who underwent a bilateral 3-wall decompression (lateral, medial and inferior walls). Nine eyes (18.0%) showed a 6 mm reduction, 2 of which received a balanced deep lateral and medial wall decompression while the remaining 7 eyes, a 3-wall decompression. Twenty-eight eyes (58.0%) showed 4-5 mm reductions, 16 of which had medial and inferior wall decompression, 2 eyes with balanced deep lateral and medial wall decompression and 10 eyes with a 3-wall decompression.

Improvements in diplopia Overall, there were a certain degree of improvements in double vision, for 8 cases (32.0%) declared that symptoms greatly improved, and these patients revealed approximately an 8-15 PD reduction in deviation. In contrast, 3 cases (12.0%) complained emerging double vision and developed strabismus (approximately 10-15 PD) 6-48mo after OD surgery, of which 1 case received decompression of the deep lateral and inferior walls, 2 cases with a 3-wall decompression. However, ocular motility improved in 12 cases (48.0%), with a 25%-50% improvement in the restricted direction (P<0.01).

Complications Two patients (8.0%) showed increased upper eyelid retraction after OD, which was corrected by subsequent tarsorrhaphy. Newly-developed strabismus was observed in 3 cases (12.0%). No other complications occurred in our case series.

DISCUSSION

To date, the management of very severe TAO, especially DON is still a matter of controversy among ophthalmologists[11]. Although a number of studies have provided findings on the efficacy and safety of various treatments for TAO, only a few studies with small sample size have been directed to the reliable treatments for sight-threatening TAO[7,11]. As a result, many issues relating to the treatment of this serious disease remained to be addressed. In addition, some studies are advocating a comparatively low-dose ivGC plan and immediately OD surgery in case of potentially life-threatening adverse effects when it comes to the arrangement of moderate-to-severe TAO without clearly demarcating DON or detailing the general conditions[8]. Currently, no clear information regarding the optimal dose and administration protocol of systemic high-dose ivGC therapy for these sight-threatening TAO is available. Moreover, the specific indications for orbital decompression, details regarding surgical techniques employed and surgical effects warrant further evaluation.

van Geest *et al*[9] reported results obtained from their severe TAO patients who received intravenous 0.5 g/d methylprednisolone for 3d every week for a total of 4wk. They found that this treatment produced a reduction in CAS scores with improvements in double vision, swelling of soft tissue, eye movement and exophthalmos, however ~33% of these patients relapsed and required OD. In Higashiyama *et al*'s study[10], 17 patients received intravenous methylprednisolone at 0.5-1.0 g/d for 3d every week for 4wk (a cumulative dose ≤8 g), followed by oral prednisone at 30-40 mg/d as a maintenance treatment. In these patients, edema within the extraocular muscles was greatly reduced and CAS scores were substantially decreased. However, this protocol had little effects on patients with sight-threatening TAO that with DON and/or severe corneal exposure[10]. Liu *et al*[12] treated their severe TAO subjects with intravenous methylprednisolone at 0.5-1.0 g every other day for a total of 3wk. With this regimen their patients improved on CAS score reduction, visual acuity, exophthalmos and eye movement, with a cure rate of 40%-50%. EUGOGO[8] summarized the results of 30 clinical studies and recommended the following guidelines for ivGC therapy: an initial dose of 0.5 g/wk (0.75 g for severe cases) methylprednisolone for 6wk, followed by 0.25 g/wk (0.5 g for severe cases) for 6wk. The cumulative dose resulting from this protocol was 4.5 g (or 7.5 g for severe case)[8] with an overall effective rate of 79.9%-82.6%[13]. However, as these studies were limited to patients from European countries, there remains the issue as to whether they would be applicable to other regions. For example, there is evidenced from studies as performed with Asian patients which show that a cumulative dose of 9-12 g methylprednisolone resulted in higher remission rates, but relatively more side effects, while a cumulative dose of 4.5-6 g methylprednisolone proved to be effective with minor side effects[14-15].

Patients in our study treated steroid pulse therapy only showed obvious improvements in CAS scores, visual acuity, ocular alignment and ocular motility, while changes in exophthalmos were not so remarkable, effects which were similar to that reported in previous studies. In specific, 41 cases (68.3% of ivGC group) showed severely impaired visual functions, significant exophthalmos and obvious hypertrophy of extraocular muscles. According to the recommended guidelines, these patients should receive OD surgery. However, after ivGC therapy, they achieved satisfactory results and were able to avoid surgical intervention. In this way, ivGC therapy can be as effective as OD for recovery of optic nerve function in some cases[16].

OD, as achieved through removal of either the orbital wall or orbital fat, is a cornerstone in the treatment of very severe TAO, especially those diagnosed with DON[6]. Bony decompression includes a balance of medial and lateral walls, deep lateral wall, inferomedial wall, or "3-wall" (medial, lateral, inferior wall) techniques. Fatty decompression is commonly used due to its lower complication rate[8,17]. OD are required for those patients who are unresponsive to ivGC or radiotherapy, and proves effective for correcting exposure keratopathy, restoring optic nerve function as well as for disfiguring exophthalmos[18]. The specific surgical methods to be used for OD are selected by the surgeon depending on the TAO severity. A deep lateral orbit wall combined with fatty decompression are used for TAO patients with exophthalmos less than 18 mm, while the 2-wall OD (balanced medial and lateral wall or inferomedial wall) is selected for cases with exophthalmos from 18-21 mm. The 3-wall (medial, inferior and lateral wall) OD was used for patients with exophthalmos of more than 21 mm[19]. Although an extensive number of studies exist evaluating the various techniques for orbital decompression[20], there is no consensus on specific indications and type of surgical approach which is the most efficient. As compared to results obtained with ivGC therapy, OD has a definite therapeutic effect on exophthalmos reduction, along with vision improvement in 70%-80% cases[21]. However, in a well-organized randomized controlled trial, Wakelkamp *et al*[7] compared immediately OD treatment with ivGC therapy among active DON patients and came to the conclusion that the former had no advantage over the latter.

In regard to diplopia and strabismus, opinions vary. In most papers, diplopia is divided into pre-existing diplopia and new-onset diplopia. Improvement rates in pre-existing diplopia have been reported from 20% to 30%[22-23]. Conversely, some reports show that OD is ineffective in relieving strabismus and diplopia (range from 3% to 25%)[24-25], and around 20% of these patients require further strabismus surgery after OD at least 6mo later[26-28]. To compare diplopia changes after various OD approaches is hampered by multiple factors: the preoperative conditions of the patients[29] (diplopia in primary gaze or secondary gaze), the criteria for detecting diplopia, subjective factors of the patients, *etc*. It is said that balanced decompression considering the involvement of extraocular muscles and technique to remodel the fat medially and laterally, may contribute less worsening of diplopia and sometimes improve the existing diplopia[30]. Our results indicated that 32% of our patients treated with OD showed an improvement on diplopia. This could be explained by 1) for patients who showed a hypertropia, we often selected a decompression of the orbital floor; 2) adipose tissue removal was performed in all cases attempting to rebalance the proptosis which may also improve the deviation of the eyeball; 3) similar to ivGC therapy, patients who received OD showed obvious reduction of swelling orbital tissues, which could improve the pre-existing diplopia.

In this study, all patients in OD group initially received ivGC, but were unresponsive to this ivGC therapy. In line with previous reports, our study confirms the efficacy of OD in such conditions. After OD surgeries, all the patients obtained a mean exophthalmos reduction of 4.35±1.13 mm, with a maximum reduction of 7 mm (3-wall OD). They also showed improvements with regard to their eyelid swelling, conjunctival congestion and exposure keratitis. Four patients achieved normal vision (20/25 or 20/20) after OD surgery, but their visual acuity decreased (from 20/25 or 20/20 to 20/100) when examined at follow-up. When treated with a second regimen of ivGC therapy (0.5 g/d for 3d, followed by 40 mg/d oral prednisone for the following 4d), their vision was restored. Three cases in our study developed strabismus after OD, 2 of which received a 3-wall OD. The occurrence of post-OD strabismus has been reported since 1998[31]. Inferior-medial wall OD was reported to be comparable to a decompression of lateral and inferior walls in terms of post-OD double vision[32], and this rate was related to the number of orbital bony walls removed, with increasing rates of strabismus being associated with increasing number of orbital walls removed[33]. It was also said that opening the periorbita may lead to higher rates of new-onset diplopia[26]. Our results show that, OD produced satisfactory results in those patients who were refractory to steroids. In some patients experiencing vision loss (from 20/25 to 20/100) after successful OD, vision was restored following subsequent ivGC treatment. However, 12.0% of these patients acquired strabismus or their strabismus became more severe following OD. It is worth mentioning that there was one special case in our study who was a male with normal visual fields and visual acuity in his right eye. He received OD surgery because of the extremely high IOP (≥30 mm Hg), severe exophthalmos and progressive cornea exposure. Besides, his color vision and VEP results were already abnormal at that time. His left eye was in extremely poor conditions with finger counting visual acuity. Therefore, we took a radical measure to conduct the OD surgery in his both eyes to rescue his visual function. When examined at the final follow-up, the visual acuity in his right eye remained 20/20 while his left eye was 20/40. Both IOP return to normal (≤21 mm Hg), and no exposure keratitis occurred.

The limitations of the present study include the relatively small sample size, and that all patients were treated by a single author which precludes effects that may result from individual differences in surgical techniques of OD. As this was an uncontrolled retrospective study it is vulnerable to some clinical data bias. While comprehensive examinations of visual

functions (visual acuity, visual field, VEP and color vision) were performed prior to treatment in these cases, only visual acuity examinations were performed at the final follow-up. Finally, the fact that all patients were from south China may also limit the findings of this study. Future work on this topic will require randomized controlled trials in patients with sight-threatening TAO, especially those with DON. Comparing two or more intravenous steroid administration protocols, different surgical interventions for OD and information addressing the efficacy, safety and quality of life in these patients.

In summary, we found that the severely impaired eyesight in some patients with sight-threatening TAO could be restored by ivGC alone, thus sparing them from surgical OD. Some patients, who experienced vision loss after successful OD, showed a restoration of their vision again in response to ivGC treatment. In those patients refractory to steroids, OD often resulted in satisfactory outcomes, however, new-onset strabismus was present in 12.0% of these patients following OD surgery. Based on the findings of our review there exists compelling evidence that ivGC should be considered as a first-line treatment for active sight-threatening TAO, while subsequent OD is particularly effective in cases unresponsive to steroids.

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