·Clinical Research·

Orbital decompression surgery and horse chestnut seed extract improved superior orbital vein blood flow in patients with thyroid-associated ophthalmopathy

Yu-Jie Wu, Xin Wei, Man-Yi Xiao, Wei Xiong

Department of Ophthalmology and Eye Disease Research Center, the Second Xiangya Hospital of Central South University, Changsha 410011, Hunan Province, China

Correspondence to: Wei Xiong. Department of Ophthalmology and Eye Disease Research Center, the Second Xiangya Hospital of Central South University, Changsha 410011, Hunan Province, China. weixiongdoc@126.com

Received: 2014-12-12 Accepted: 2015-02-04

Abstract

• AIM: To evaluate the efficacy and safety of orbital decomposition (OD) surgery in combination with horse chestnut seed extract (HCSE), as compared to OD alone, in patients with thyroid-associated ophthalmopathy (TAO).

• METHODS: Sixty-two orbits from 62 TAO patients were randomly assigned to OD or OD+HCSE at 1:1 ratio (31 received OD alone, 31 received OD+HCSE). Forty-two orbits from 21 healthy subjects were used as controls. Complete ophthalmic examination and color Doppler flow imaging (CDFI) were performed before surgery and 3mo post-surgery on all 62 orbits from the TAO patients. CDFI were also performed on the 42 control orbits. The effect of OD+HCSE and OD alone on TAO orbits was compared on several endpoints, including superior ophthalmic vein blood flow (SOVBF) parameters, subjective assessment, soft tissue involvement, lid retraction, diplopia, eye movement restriction, degree of exophthalmos, and intraocular pressure. The control orbits were used as reference for the SOVBF parameters.

• RESULTS: OD surgery with or without HCSE improved SOVBF, symptoms and soft tissue involvement, decreased degree of exophthalmos and intraocular pressure in orbits of TAO patients. The OD+HCSE combination led to significantly better improvement of SOVBF than OD alone. The differences between the reductions of SOVBF in the two groups are 1.26 cm/s in max-volecity and 0.52 cm/s in min-volecity (P<0.0001).

• CONCLUSION: SOVBF is significantly reduced in the orbits affected with TAO, indicating that congestion may be an important factor contributing to TAO pathogenesis. OD surgery improves the SOVBF, and combination of HCSE medication and OD surgery further improved venous return than OD surgery alone.

• **KEYWORDS:** thyroid-associated ophthalmopathy; color Doppler flow imaging; superior orbital vein; orbital decompression; horse chestnut seed extract

DOI:10.18240/ijo.2016.06.14

Wu YJ, Wei X, Xiao MY, Xiong W. Orbital decompression surgery and horse chestnut seed extract improved superior orbital vein blood flow in patients with thyroid-associated ophthalmopathy. *Int J Ophthalmol* 2016;9(6):869-875

INTRODUCTION

Thyroid-associated ophthalmopathy (TAO) is an autoimmune inflammatory process that affects the periorbital and orbital tissues, mainly the extraocular muscles and orbital fat [1]. The inflammation of these tissues contributes to most of the manifestations of the diseases[2-3]. The degree of TAO severity can be classified as mild, moderate to severe and sight-threatening based on the quantitative assessment of some signs [4-5]. The early stage of TAO is the active stage, *i.e.* congestive or inflammatory stage. The end-stage is the non-mobile stage, *i.e.* fibrotic stage[6-8]. Clinical activity score is usually used to evaluate the activity of TAO. Whether it is due to autoimmunity or due to congestion, tissue inflammation as demonstrated by the computer-aided tomography [9-11] and color Doppler flow imaging (CDFI)[12-15], may lead to the same clinical diagnosis of the early active stage. However, choice of the treatment and its prognosis would be different depending on which cause, *e.g.* glucocorticoids would be effective for autoimmune inflammation but not as much for congestion. Currently, no objective index exists that can be used to distinguish the inflammation predominantly caused by autoimmunity from that predominantly caused by congestion. Superior orbital vein (SOV) is the main vessel that guides the blood backflow of orbital tissues. Several recent studies have used CDFI to demonstrate that SOV flow was significantly reduced in orbits with congestive TAO [12-16]. These studies lend support to the notion that venous congestion plays a significant role in the pathogenesis in the active stage of the orbitopathy and suggest that TAO patients

could benefit from relief of SOV congestion by medical and/or surgical treatments. Orbital decomposition (OD) surgery was initially used to treat severe exophthalmos with exposure keratitis and oppressive optic neuropathy. Recently, more and more TAO patients have accepted OD to improve their cosmetic appearance[17-20]. It has been suggested that OD can ameliorate the blood backflow of SOV to alleviate the swelling of orbital tissues [21-22]. To our knowledge, however, no study has been conducted to evaluate the CDFI flow parameters in patients with congestive orbitopathy receiving treatment of OD in combination with a medicine to ameliorate the blood backflow. Horse chestnut seed extract (HCSE) is a medication used to ameliorate the venous backflow. It normalizes the permeability of the venous wall, prevents the leakage of fluid into the surrounding tissues and thus, counteracts the development of an edema. With pre-existing edema, it stimulates excretion of water and helps reduce swelling. One tablet of HCSE is 150 mg and equal to 30 mg three iridoid glycoside. The pharmacological action of HCSE is to obviously inhibit the activity of lysosomes in serum by stabilizing lysosomal membrane stability and blocking the metabolism of proteasomes.

The purpose of this study was to evaluate the effectiveness of OD with or without HCSE on improvement of SOV blood flow parameters measured by CDFI, subjective assessment (symptoms) and signs in TAO patients before and after treatment.

SUBJECTS AND METHODS

Study Design This open-label, prospective, interventional, randomized and comparative study was conducted between April 2009 and October 2012. The study followed the principles of the Declaration of Helsinki. Approval from the Ethics Committee of the Second Xiangya Hospital of Central South University was obtained, and all of the participants gave their informed consents.

A total of 62 patients (20 men and 42 women) with TAO were recruited. Assuming a standard deviation of 0.9 in post-surgery change from baseline in superior ophthalmic vein blood flow (SOVBF), 31 subjects per group will provide at least 91% power to detect a treatment difference of 0.75 between OD+HCSE and OD group at a two-sided significance level of 0.05.

Before the treatment, the degree of severity of each patient was moderate to severe and the duration of orbitopathy of each patient was more than two years. The diagnosis of TAO was established according to the previously published criteria [2]. If the patients were hyperthyroid or hypothyroid, they were treated to become euthyroid 3mo, before randomization. After screening and baseline assessment, the patients were randomly assigned into two groups receiving either OD alone or OD+HCSE combination in an open-label manner.

Surgical Procedure and Ophthalmic Examinations The patients received a complete ophthalmic examination including evaluation of eyelid and conjunctiva inflammation (pain, congestion and edema), measurement of the lid fissure, hertel exophthalmometry, extraocular motility evaluation, best corrected visual acuity, applanation tonometry, pupillary reactions, slit lamp examination, fundoscopy, and visual field evaluation with standard automated perimetry using the ZEISS Humphrey Field Analyzer 750I (Carl-Zeiss Meditec, Dublin, CA, USA). Both orbits of the patients were scanned with 16-slice multi-detectors with a computer-aided tomography scanner (Brilliance 16; Philips Medical Systems, Nederland B.V., the Netherlands). After the ophthalmic examination, the patients received CDFI with Voluson® E8, an instrument made by General Electric (Austria). Maximum and minimum blood flow in the SOV was determined in both eyes while the patients were resting on a bed with head being elevated for 30 degrees. During the examination, the patients were requested to remain still with both eyes closed and fixated straight ahead. The transducer was gently placed over the closed eyes (right eye first), and care was taken to avoid applying pressure to the eyes. Blood flow velocity was measured in the superior nasal part of the SOV, anterior to the point where it crosses the optic nerve. Velocity was measured in each vessel several times until at least two good readings were obtained, with the angle between the sound beam and the blood flow direction being kept under 30 degrees. CDFI was performed on a total of 104 orbits, including 42 from the 21 normal control subjects, 31 from the group-A TAO patients before treatment and 31 from the group-B TAO patients before treatment. All CDFI measurements were performed by the same experienced professional ultrasonographer who was blinded to the clinical status of the patients. Maximum and minimum SOV blood flow velocities (Vmax and Vmin) were recorded, and the differential flow (DF) was derived by taking the difference between Vmax and Vmin. Each group of orbits was initially classified according to whether the flow in the SOV was anteroposterior, absent (not detected), or posteroanterior (reversed). The observed proportions were compared using Fisher's exact test. For further statistical analyses using parametric methods, the anteroposterior flow was expressed in positive numbers, the undetected flow was assigned a value of zero, and the posteroanterior flow was expressed in negative numbers.

All patients received treatment of one-sided orbit with two-wall OD, which included inside wall decompression under nasal sinuses endoscope and lateral wall decompression. Three days after the operation, patients of group A did not take HCSE. The patients of the group-B took HCSE (300 mg *b.i.d*) orally for 3mo. No surgical or medical treatment was performed on the normal control patients.

The complete ophthalmic and CDFI examinations were repeated 3mo after the operation. Patients' safety was monitored during study period until the last follow up visit.

Study Endpoints The primary efficacy endpoint was the change from baseline in maximal and minimal values of the SOVBF after OD or OB+HCSE treatment. The secondary endpoints included subjective assessment, soft tissue involvement, lid retraction, diplopia, eye movement restriction, degree of exophthalmos, intraocular tension. Safety endpoints included impaired vision or blindness, intraorbital hematoma and/or infection, as well as the overall health status of the patients.

Statistic Analysis Statistical analyses were performed using the SAS® Version 9.2 (Raleigh, NC, USA). The descriptive statistics included mean values and standard deviation (SD) or standard errors (SE) for continuous variables. Histograms, univariate analysis and the Shapiro-Wilk test were used to check the validity of the normality assumption. One-way ANOVA was performed on the pre-surgery values of SOVBF among the groups A (the OD treatment group), B (the OD+HCSE treatment group), and C (the normal control group), followed by pairwise comparisons between A and C, B and C using the Fisher's least significant difference method to control type I error rate for multiple testing. Similar analyses were also done on the post-surgery values of SOVBF of the A and B groups and the control values of the C group. Moreover, paired t-tests were done to evaluate the treatment effect of the OD and OD+HCSE respectively. The post-surgery change from baseline in the group B was compared to that of group A by two-sample t test to compare the treatment effects between the two groups. All above analyses were done for the Vmax, Vmin, and DF respectively.

Sensitivity analysis was also conducted on the SOVBF variables by using non-parametric methods such as Kruskal-Wallis test and Wilcoxon Rank-sum test and the results were similar to the above results from parametric analyses.

For other variables, appropriate statistical methods were used depending on categorical variable or continuous variable. See results section for details.

A P value of less than 0.05 was considered statistically significant. Multiplicity was controlled where necessary.

RESULTS

Baseline Demographics and Characteristics The mean age of the 31 patients (10 men and 21 women) of the OD group (group A) was 56.8±10.5y. The mean age of 31 patients (10 men and 21 women) of the OD+HCSE group (group B) was 58.2±11.4y. The baseline demographics and characteristics of the TAO patients in each group are listed in Table 1. In comparison to the TAO patients, twenty one subjects (7 men and 14 women, aged 59.3±9.9y) healthy euthyroid volunteers without ocular diseases were selected as a control group (group C). There was no significant age difference between the TAO patients and normal control subjects (P=0.352).

Table 1 Baseline demographics and characteristics $\bar{x} \pm s$

Characteristics	Group A	Group B	Group C	P
Age (a)	56.8±10.5	58.2±11.4	59.3±9.9	0.352
Gender (n)				
M	10	10	7	
F	21	21	14	
SOVBF velocity (cm/s)				
Max	2.81±0.67	2.75±0.67	7.13±0.57	<0.0001
Min	1.81±0.44	1.72±0.44	4.72±0.38	<0.0001
DF	1.01±0.29	1.03±0.29	2.41±0.25	0.0002

Group A: TAO patients randomized into OD treatment; Group B: TAO patients randomized into OA+HCSE treatment; Group C: Healthy control subjects. P<0.001 for group A compared to group C for Vmax, Vmin and DF. P<0.001 for group B compared to group C for Vmax, Vmin and DF.

Primary Endpoints

Superior ophthalmic vein blood flow SOV is the chief vessel that guides the blood backflow of orbital tissues. In the normal control subjects, SOV blood flow was detected in 38 orbits but not in 4 orbits. Reverse blood flow was not observed. In orbits with TAO before OD, SOV flow was absent in 5, present in 21 and reversed in 5 orbits before treatment (Table 2). After OD treatment, SOV flow was absent in 3, present in 28 and reversed in 0 orbits. These data indicate that OD can significantly improve the venous flow of SOV. In the orbits with TAO before OD+HCSE, SOV flow was absent in 5, present in 21 and reversed in 5 orbits before treatment. After treatment, SOV flow was absent in 5, present in 26 but not reversed in any orbits. These results indicate that OD+HCSE can remarkably improve the venous flow of SOV. A significant difference was found between the two groups of TAO orbits before treatment and the control orbits. However, no significant difference was found between the two groups of TAO orbits after treatment and the control orbits. No significant difference was found between two groups of TAO orbits before or after treatment.

The SOVBF velocity (Vmax, Vmin and DF) data are illustrated in Figure 1 and the descriptive statistics and P values are presented in Tables 1 and 3. At the baseline (Table 1), the Vmax, Vmin and DF were all significantly decreased in the TAO group A or group B as compared to the normal controls (P<0.001 for the ANOVA F test and post-hoc t tests between both groups and the Control group for all three variables). These results indicated a significant reduction in SOV blood flow in TAO group of patients. After OD or OD+HCSE treatment, the values of Vmax, Vmin and DF in TAO were quite similar to the corresponding values of the normal control group and the ANOVA F tests were not significant for all three variables (P>0.1). The paired t-tests in both groups A and B were

Table 2 Detection and direction of blood flow in the SOV using CDFI in patients with TAO and control subjects *n* (%)

Groups	SOV blood flow			
	Anteroposterior	Posteroanterior (reverse)	Not detected	No. of orbits
Controls	38 (90.5)	0 (0.0)	4 (9.5)	42 (100)
TAO before OD	21 (67.8)	5 (16.1)	5 (16.1)	31 (100)
TAO after OD	28 (90.3)	0 (0.0)	3 (9.7)	31 (100)
TAO before OD plus HCSE	21 (67.8)	5 (16.1)	5 (16.1)	31 (100)
TAO after OD plus HCSE	26 (83.9)	0 (0.0)	5 (16.1)	31 (100)

Fisher's exact test (P=0.003, controls compared with TAO before OD; P=0.003, controls compared with TAO before OD plus HCSE). Fisher's exact test (P=0.597, controls compared with TAO after OD; P=0.622, controls compared with TAO after OD plus HCSE).

Table 3 SOVBF velocity (cm/s) post-treatment comparisons $\bar{x} \pm s$

SOV blood flow	Group A	Group B	Group C	P
3mo post-surgery				(F test)
Max	6.47±0.64	7.67±0.64	7.13±0.57	0.4175
Min	4.29±0.45	4.71±0.45	4.7±0.38	0.7280
DF	2.18±0.27	2.96±0.27	2.41±0.25	0.1151
Change from baseline				(Paired t test)
Max	3.66±0.19	4.92±0.40	N/A	<0.0001
Min	2.48±0.16	3.00±0.19	N/A	<0.0001
DF	1.18±0.22	1.93±0.29		<0.0001
Change from baseline	Group B *vs* group A			(2-sample t test)
Max	1.26±0.44			<0.0001
Min	0.52±0.25			<0.0001
DF	0.75±0.36			0.043

Group A: TAO patients randomized into OD treatment; Group B: TAO patients randomized into OA+HCSE treatment; Group C: Healthy control subjects. P<0.0001 for group A change from baseline for Vmax, Vmin and DF. P<0.0001 for group B change from baseline for Vmax, Vmin and DF. P<0.0001 for group B *vs* group A comparison of change from baseline in both Vmax, and Vmin. P=0.043 for group B *vs* group A comparison of change from baseline in DF.

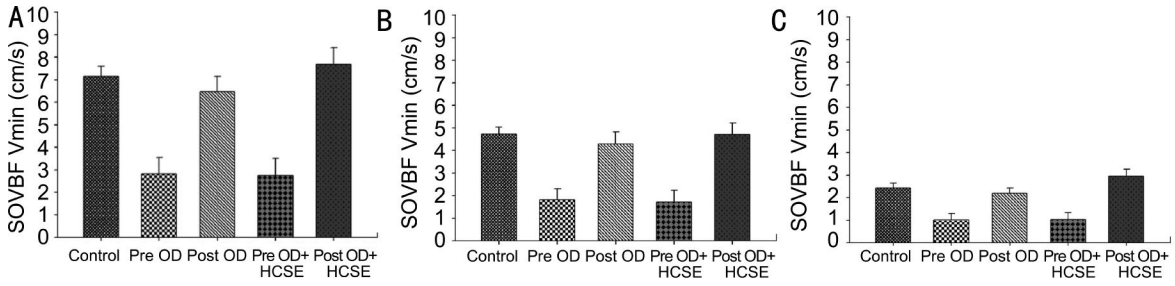

Figure 1 Plots of means and SE of the Vmax, Vmin and DF for control, pre OD, post OD, pre OD+HCSE and post OD+HCSE.

significant for all three variables (P<0.0001), indicating that both OD and OD+HCSE significantly improved the SOV blood flow. Furthermore, the comparisons between groups A and B in terms of change from baseline in all three variables were statistically significant (P=0.043), suggesting that OD+HCSE further improved Vmax, Vmin and DF than OD alone. Taken together, these results indicated that both OD and OD+HCSE recovered the decreased SOVBF back to normal levels while OD+HCSE led to statistically significantly better improvement than OD alone.

Secondary Endpoints

Subjective assessment and soft tissue involvement In group A, 22 patients (71%) subjectively reported improvement of symptoms, 4 patients experienced deterioration of symptoms (two worsening of congestion and two new diplopia) and 5 cases felt no difference after OD. In group B, 24 patients (77%) subjectively reported improvement of symptoms, three patients experienced a deterioration of symptoms (two worsening of congestion and one with new diplopia) and 4 cases felt no difference after OD+HCSE. These results indicated that both OD and OD+HCSE improved the symptoms, although there was no significant difference between the 2 groups (Fisher's exact test: P=0.521).

While there was no quantitative way to measure the edema and swelling of soft tissue (eyelid or conjunctiva), improvement after treatment was observed in most of the

patients (24 patients in group A and 28 in group B), as demonstrated by the contrast in the pictures taken before treatment and 3mo after treatment.

Lid retraction, diplopia and eye movement restrictions Quantitative measurement of the lid fissure was performed to evaluate lid retraction. There was no obvious change on lid retraction after treatment and further minor cosmetical operation was performed on some patients.

Before the treatment, most of the patients had varying degree of diplopia (intermittent diplopia: present when the patients were fatigued; inconstant diplopia: present at extremes of gaze; constant diplopia: present in primary gaze). There was no significant improvement 3mo after treatment.

Eye movement restrictions in the field of action of the superior rectus muscle (elevation) due to inferior rectus restriction and of the lateral rectus muscle (abduction) due to medial rectus restriction were graded from 0 (no limitation) to 4 (absence of eye movement from primary position in the muscle's field of action). Grades 1, 2 and 3 restrictions indicated 75%, 50%, and 25% excursion, respectively, from the primary position, either by elevation (restriction caused by the inferior rectus) or by abduction (restriction of the medial rectus). A combined restriction index ranging from 0 to 8 was calculated by adding the two scores. However, there was no significant improvement on eye movement restrictions after treatment.

Degree of exophthalmos To decrease the degree of exophthalmos is one of the aims of various therapeutic methods for TAO. The effects of OD and OD+HCSE on decreasing the degree of exophthalmos in TAO patients were also examined and the results were presented in Table 4. Both OD and OD+HCSE appeared to remarkably decrease the degree of exophthalmos after treatment. However, the differences between the two treatments in decreasing the degree of exophthalmos was not statistically significant (Fisher's exact test: P=0.438).

Intraocular pressure The increase in intraocular pressure (IOP) is one of the signs of TAO, which is caused by the obstruction of venous return. We examined the effects of both OD and OD+HCSE on decreasing the IOP in TAO patients and the results were presented in Table 5, which clearly showed that both OD and OD+HCSE decreased the IOP but there was no statistically significant difference between OD+HCSE and OD alone (Fisher's exact test: P=0.372).

Safety Endpoints Although the risks of HCSE are infrequent, it may contain significant risk for the patients who use anti-coagulants. No patients in this study used anti-coagulants and monitoring of platelets and prothrombin time was used for each patient every other month. There was no safety issue with either treatment. The patients' overall health status in the OD and OD+HCSE groups were comparable before or after treatment.

Table 4 Decreasing the degree of exophthalmos after OD and OD plus HCSE treatments n=31 cases, n (%)

Decreasing degree	≤2 mm	3-4 mm	≥5 mm	P
TAO after OD	2 (6.4)	10 (32.3)	19 (61.3)	0.438
TAO after OD+HCSE	2 (6.4)	9 (29.0)	20 (64.6)	

Table 5 Decreasing degree of the IOP after OD and OD plus HCSE treatments n=31 cases, n (%)

Decreasing degree of IOP	≤2 mm Hg	3-4 mm Hg	≥5 mm Hg	P
TAO after OD	10 (32.3)	18 (58.1)	3 (9.6)	0.372
TAO after OD+HCSE	8 (25.8)	19 (61.3)	4 (12.9)	

DISCUSSION

Autoimmunity is likely the primary mechanism involved in the pathogenesis of TAO. A number of clinical and experimental findings have suggested that orbital venous blood flow congestion contributes to the development of clinical signs and symptoms (*e.g.* proptosis, muscle restriction, periorbital swelling, and chemosis) during the active stage of this disease [21,23]. Previous studies have indicated that experimentally induced orbital venous stasis could closely mimic many of the clinical changes that occur in TAO [23] and that the existence of severe venous stasis in the orbits may be related to the development of dysthyroid optic neuropathy[12]. Doppler parameters of maximal velocity in SOV appear to be helpful in the differentiation of active phase from inactive phases of Graves' ophthalmopathy [24]. The decrease in SOV-BFV increases the severity of Graves' orbitopathy [25]. OD surgery was shown to promptly improve the congestive signs of TAO patients [21]. All of these studies have indicated that orbital venous stasis (especially stasis of the SOV which is the main vein in the orbit) is also an important mechanism involved in the TAO pathogenesis. Thus improvement of orbital venous stasis could be an effective approach to treating TAO. OD is a very effective method to improve the SOV-BFV and ameliorate the clinical signs and symptoms of TAO. In this study, we not only confirmed the effectiveness of OD, but also for the first time applied HCSE in combination with OD and demonstrated better efficacy by OD+HCSE than OD alone in promoting venous return, suggesting OD+HCSE could be a better way to treat TAO than OD alone.

CDFI allows simultaneous imaging of the anatomic structures by B-mode ultrasonography with superimposed color-coded vascular flow. The current study confirmed a significant difference in CDFI parameters between orbits with TAO before treatment and controls or orbits with TAO following treatment. Reversed and absent blood flows were observed in 5 each out of 31 orbits with TAO group A before treatment, respectively. Similarly, reversed and absent blood flows were observed in 5 each out of 31 orbits with TAO group B before treatment, respectively. After treatment, the reverse of blood flow was corrected, and the blood flow was significantly increased to a level that was

similar to the healthy control group, suggesting that venous congestion is the most likely factor contributing to the pathogenesis of this condition. Our data showed that SOV maximum velocity, SOV minimum velocity and DF velocity were all significantly lower in TAO than those in controls or TAO after treatment, which are consistent with results from several previous studies [12,16,21]. These findings strongly indicated the existence of severe venous stasis in the orbits of TAO. Previous studies have shown the effectiveness of OD in raising the velocity of SOV [21-22]. We conducted this study to test the hypothesis that adding a medication HCSE to OD would further improve the venous return and the TAO outcome. Indeed, our results have demonstrated that all SOV velocity parameters (Vmax, Vmin and DF) after OD+HCSE were significantly higher than that after OD alone, confirming our hypothesis.

We also evaluated the amelioration of the symptoms and signs, and the improvement in the quality of life for the patients. The subjective assessment and soft tissue were improved after treatment with OD or OD+HCSE because both ameliorated the venous flow and decreased the edema of soft tissues. However, lid retraction, diplopia and eye movement restriction were not improved, which can be explained by the fact that the duration of orbitopathy was more than one year and the muscles (levator muscle of upper eyelid and extraocular muscles) have been fibrotic.

To decrease the degree of exophthalmos is one of the aims of various therapeutic methods to treat TAO, especially for cosmetic enhancement. All other methods except OD are ineffective for those patients in active stage caused by congestion or in fibrotic stage. However, OD with or without HCSE significantly decreased the degree of exophthalmos.

The increasing IOP, mainly caused by the obstruction of venous return, is one of the signs of TAO. Our data showed that OD with or without HCSE remarkably decreased the IOP.

There are certain limitations of our study. A blind, placebo-controlled study design would have been better to reduce the potential bias. However, due to practical reasons, this study was conducted as an open-label study without placebo control.

In conclusion, the CDFI data obtained in this study and previous studies may be useful for the management of TAO. Traditional treatment of TAO in the acute stage using corticosteroids, immune-suppressant or radiotherapy is immunosuppressive. However, corticosteroids may be contraindicated in some patients while radiotherapy may not be available in some hospitals/clinics. Moreover, congestive signs sometimes remain despite adequate treatment and may require OD to get cosmetic effect. Thus, persistently reduced or reversed SOV blood flow despite adequate treatment may be an indication for OD in certain TAO patients. Furthermore, adding a drug (such as HCSE) to OD for promoting venous return is also helpful to effectively improve the outcome.

ACKNOWLEDGEMENTS

We would like to acknowledge Dr. Xuejun Victor Peng, a professional statistician who received his PhD in Statistics in 2003 in the United States, for his advice and support on the statistical analysis, interpretation of the results, as well as editing the manuscript.

Conflicts of Interest: Wu YJ, None; **Wei X,** None; **Xiao MY,** None; **Xiong W,** None.

REFERENCES

1 Regensburg NI, Wiersinga WM, Berendschot TT, Potgieser P, Mourits MP. Do subtypes of graves' orbitopathy exist? *Ophthalmology* 2011;118(1):191-196.

2 Bartley GB, Gorman CA. Diagnostic criteria for Graves' ophthalmopathy. *Am J Ophthalmol* 1995;119(6):792-795.

3 Bartley GB, Fatourechi V, Kadrmas EF, Jacobsen SJ, Ilstrup DM, Garrity JA, Gorman CA. Clinical features of Graves' ophthalmopathy in an incidence cohort. *Am J Ophthalmol* 1996;121(3):284-290.

4 Bartalena L, Baldeschi L, Dickinson AJ, *et al*. Consensus statement of the European group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy. *Thyroid* 2008;18(3):333-346.

5 Stan MN, Garrity JA, Bahn RS. The evaluation and treatment of graves ophthalmopathy. *Med Clin North Am* 2012;96(2):311-328.

6 Fan XQ. *Ophthalmic plastic and reconstructive surgery*. Beijing Science and Technology Press;2009;584.

7 Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Berghout A, van der Gaag R. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach. *Br J Ophthalmol* 1989;73(8):639-644.

8 Bartalena L, Pinchera A, Marcocci C. Management of Graves' ophthalmopathy: reality and perspectives. *Endocr Rev* 2000;21(2):168-199.

9 Monteiro ML, Goncalves AC, Silva CT, Moura JP, Ribeiro CS, Gebrim EM. Diagnostic ability of Barrett's index to detect dysthyroid optic neuropathy using multidetector computed tomography. *Clinics (Sao Paulo)* 2008;63(3):301-306.

10 Hudson HL, Levin L, Feldon SE. Graves exophthalmos unrelated to extraocular muscle enlargement. Superior rectus muscle inflammation may induce venous obstruction. *Ophthalmology* 1991;98(10):1495-1499.

11 Nugent RA, Belkin RI, Neigel JM, Rootman J, Robertson WD, Spinelli J, Graeb DA. Graves orbitopathy: correlation of CT and clinical findings. *Radiology* 1990;177(3):675-682.

12 Nakase Y, Osanai T, Yoshikawa K, Inoue Y. Color Doppler imaging of orbital venous flow in dysthyroid optic neuropathy. *Jpn J Ophthalmol* 1994;38(1):80-86.

13 Alp MN, Ozgen A, Can I, Cakar P, Gunalp I. Colour Doppler imaging of the orbital vasculature in Graves' disease with computed tomographic correlation. *Br J Ophthalmol* 2000;84(9):1027-1030.

14 Somer D, Ozkan SB, Ozdemir H, Atilla S, Soylev MF, Duman S. Colour Doppler imaging of superior ophthalmic vein in thyroid-associated eye disease. *Jpn J Ophthalmol* 2002;46(3):341-345.

15 Monteiro ML, Angotti-Neto H, Benabou JE, Betinjane AJ. Color Doppler imaging of the superior ophthalmic vein in different clinical forms of Graves' orbitopathy. *Jpn J Ophthalmol* 2008;52(6):483-488.

16 Benning H, Lieb W, Kahaly G, Grehn F. Color duplex ultrasound findings in patients with endocrine orbitopathy. *Ophthalmologe* 1994;91(1):

20-25.

17 Xiao LH. Reappraise the value of orbital decompression for thyroid associated ophthalmopathy. *Zhonghua Yan Ke Za Zhi* 2012;48(8):673-675.

18 Boboridis KG, Bunce C. Surgical orbital decompression for thyroid eye disease. *Cochrane Databasc Syst Rev* 2011;7(12):CD007630.

19 Longueville E. Orbital decompression in Grave's ophtalmopathy. *Rev Laryngol Otol Rhinol (Bord)* 2010;131(2):145-152.

20 Boboridis KG, Gogakos A, Krassas GE. Orbital fat decompression for Graves' orbitopathy: a literature review. *Pediatr Endocrinol Rev* 2010;7 Suppl 2:222-226.

21 Monteiro ML, Moritz RB, Angotti Neto H, Benabou JE. Color Doppler imaging of the superior ophthalmic vein in patients with Graves' orbitopathy before and after treatment of congestive disease. *Clinics (Sao Paulo)* 2011; 66(8):1329-1334.

22 Pérez-López M, Sales-Sanz M, Rebolleda G, Casas-Llera P, González-Gordaliza C, Jarrín E, Muñoz-Negrete FJ. Retrobulbar ocular blood flow changes after orbital decompression in Graves' ophthalmopathy measured by color Doppler imaging. *Invest Ophthalmol Vis Sci* 2011;52 (8):5612-5617.

23 Saber E, McDonnell J, Zimmermann KM, Yugar JE, Feldon SE. Extraocular muscle changes in experimental orbital venous stasis: some similarities to Graves' orbitopathy. *Graefes Arch Clin Exp Ophthalmol* 1996;234(5):331-336.

24 Yanik B, Conkbayir I, Acaroglu G, Hekimoglu B. Graves' ophthalmopathy: comparison of the Doppler sonography parameters with the clinical activity score. *J Clin Ultrasound* 2005;33(8):375-380.

25 Konuk O, Onaran Z, Ozhan Oktar S, Yucel C, Unal M. Intraocular pressure and superior ophthalmic vein blood flow velocity in Graves' orbitopathy: relation with the clinical features. *Graefes Arch Clin Exp Ophthalmol* 2009;247(11):1555-1559.