

Therapeutic difference between orbital decompression and glucocorticoids administration as the first-line treatment for dysthyroid optic neuropathy: a systematic review

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Abstract

• To assess all available data to compare the efficacy of glucocorticoids treatment and orbital decompression for dysthyroid optic neuropathy (DON). PubMed, EMBASE, the Cochrane Library databases as well as other sources were searched by two independent reviewers followed by extensive hand-searching for the identification of relevant studies. The primary outcomes were the improvement in visual acuity and responder rate. Secondary outcomes were the proptosis reduction, change in diplopia, and clinical activity score (CAS). One randomized controlled trial, three retrospective case series and one prospective case series met the inclusion criteria. They were divided into intravenous high-dose glucocorticoids (ivGC) group and orbital decompression (OD) group. Both groups demonstrated improvement in visual acuity. In addition, the proportion of patients with improved vision in OD group was higher than that in ivGC group ($P < 0.001$). Post-treatment proptosis reduction was also reported in both groups. Overall, weighted mean in proptosis reduction estimated at 1.64 and 5.45 mm in patients treated with ivGC and OD respectively. This study also presented results regarding pre-existing and new-onset diplopia. Apart from diplopia, a wide variety of minor and major complications were noted in 5 included studies. The most common complication in ivGC group and OD group was Cushing's syndrome and epistaxis respectively. The present systematic review shows that both

glucocorticoids treatment and OD are effective in treating DON and OD may work better in improving visual acuity and reducing proptosis. However, high-quality, large-sample, controlled studies need to be performed in the future.

• **KEYWORDS:** dysthyroid optic neuropathy; glucocorticoid; orbital decompression

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INTRODUCTION

Dysthyroid optic neuropathy (DON), secondary to thyroid-associated ophthalmopathy (TAO), is the most common cause of visual loss in TAO^[1], whose incidence is 4% to 8% among TAO patients^[2]. So far, the exact pathogenesis of DON remains unclear. Admittedly, DON is a condition that the crowding of the orbital apex leads to optic nerve compression, causing vision loss^[3]. Besides common manifestations of TAO, other clinical features of DON include dyschromatopsia, visual acuity (VA) deterioration, papilledema, visual field anomalies, folded choroid and afferent pupillary defects. Imaging examination often indicates severe orbital apex congestion^[4]. The treatment of DON mainly includes drug decompression, radiotherapy^[5-6] and surgical decompression. Steroid is most commonly applied in drug decompression^[7]. Other drugs include methotrexate (MTX)^[8], TNF- α ^[9], rituximab^[10], tocilizumab^[11], and rapamycin^[12]. All of them achieve the purpose of decompression by reducing the inflammation of the orbit and the swelling of the orbital contents while surgical decompression relieves the compression of optic nerve by removing orbital bone wall or orbital fat to increase orbital volume or reduce the volume of eye contents. Currently, the majority of the literature supports initial treatment of DON with high dose intravenous steroids^[4]. If the response is poor

or when high dose steroid therapy is not tolerated, surgical decompression is recommended. However, deviations from this management strategy were documented^[13] and there is no consensus on the treatment of DON with high-dose steroids or direct surgical decompression^[14]. Hence, most studies have reported results of mainly combined approaches while only a few have been conducted evaluating the effectiveness and the safety of purely surgical decompression or purely steroid treatment.

This study summarizes the current evidence-based medicine data, aiming to assess the outcomes of purely orbital decompression (OD) and purely steroid treatment.

MATERIALS AND METHODS

Search Strategy We searched PubMed, EMBASE, the Cochrane Library databases for publications from January 2000 to March 2020. The search was restricted to humans and only articles published in English were included in the study. The references of all retrieved studies and review papers were also carefully hand-searched.

Inclusion and Exclusion Criteria The study selection process was executed independently by two reviewers. In case of uncertainty, the full-text article was reviewed for eligibility. Disagreements were resolved by discussion and consensus. Studies fulfilling the following criteria were eligible for inclusion: all randomized and nonrandomized controlled studies were included, as well as prospective or retrospective case series of at least 10 decompressed orbits. Patients were diagnosed as DON between age of 18 to 80. Studies were supposed to include purely surgical decompression approaches or medical decompression with steroids. Any study evaluating combined approaches and treated by OD or steroids without interruption before was excluded from our systematic review. Reviews, conference abstracts, animal studies, studies with incomplete experimental data, and duplicate publications were excluded.

Primary Outcome Measures and Definitions The primary outcome measures of interest included improvement of VA and responder rate. Outcomes were evaluated from 1 to 6mo following intervention. Secondary outcomes in our study included proptosis reduction, change in diplopia and clinical activity score (CAS). Adverse outcomes were considered complications of steroid or OD surgery.

For the purpose of this systematic review, DON was defined as 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).

Data Extraction and Study Quality The first author, year of publication, country, study design, study population, comparison group, and outcome characteristics were extracted

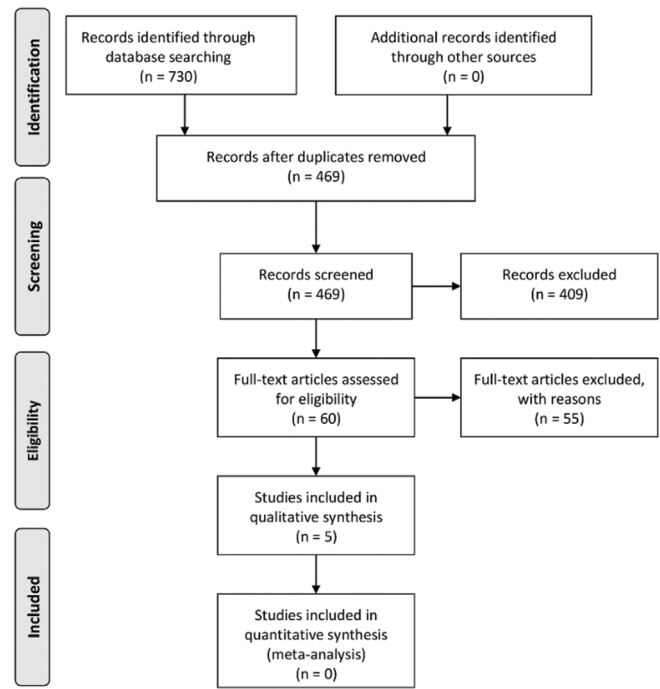


Figure 1 Prisma 2009 checklist.

by independent reviewers. The study characteristics were entered on Excel worksheets (Microsoft Corporation, Seattle, WA, USA).

The Cochrane risk-of-bias tool was used to evaluate the randomized controlled trials (RCTs) study. Case series reports using case series bias evaluation tools^[15]. The studies were classified as low, high, and uncertain risk of bias. The registration number is INPLASY202050005.

RESULTS

A total of 730 studies were retrieved through the systematic search of bibliographic databases. After removing duplicates, 469 papers were eligible for title-abstract screening. After removing duplicates, 59 were assessed for inclusion based on the full text. Ultimately, five articles^[14,16-19] were identified to answer the research question. None of the five aforementioned studies were qualified for qualitative synthesis. The flow diagram was depicted in Figure 1. There were 1 RCT, and 4 studies of case series reporting on OD surgery or steroids therapy. All included studies were written in English and published from 2000 to 2020.

A total of 155 patients (47.7% males and 52.3% females, 270 orbits) were recruited, among which 93 patients (169 orbits) were treated with intravenous high-dose glucocorticoids (ivGC) therapy and 62 patients (101 orbits) received OD. For ivGC group, the studies included shared similar therapy. Patients were treated with either 500 or 1000 mg pulsed i.v. methylprednisolone administered daily for three consecutive days. The same cycle of treatment was repeated after one week, and then steroids were tapered off either orally or intravenously in the following 4mo. The cumulative dose of

Table 1 Study characteristic

Lead author (y)	Country	Study design	Patients (n)	Sex (male/female)	Orbits (n)	Mean age (y)	Intervention	Mean follow-up (mo)	Main outcome	Baseline	Quality
Wakelkamp (2005)	Netherlands	RCT	15	2/13	15	52	ivGC, OD	ivGC:78, OD:64	VA	Similar	B ^a
Curro (2014)	Italy	Retrospective case series study	24	14/10	40	66.7	ivGC	12	VA	Similar	A ^b
Lv (2015)	China	Retrospective case series study	43	12/31	72	45	OD	9	VA	Similar	A ^b
Rajabi (2019)	Iran	Prospective study	13	6/7	23	50.48	OD	11.6	VA	Similar	A ^b
Wen (2019)	China	Retrospective case series study	60	40/20	120	49.67	ivGC	14.76	VA	Similar	A ^b

ivGC: Intravenous high-dose glucocorticoids; OD: Orbital decompression; VA: Visual acuity; RCT: Randomized controlled trial. ^aFor RCT, we used Jaded Scale to assess article quality, scores>3 was defined A, otherwise B; ^bFor case series, we used JBI critical appraisal to assess article quality, scores>14 was defined A, otherwise B.

Table 2 Primary and secondary outcomes of included studies

First author (y)	Orbits (n)	Proptosis (mm)			VA improvement (logMAR)			Diplopia	
		Pre-treatment	Post-treatment	Mean reduction	Pre-treatment	Post-treatment	Responder (n)	Report	Comment
ivGC									
Wakelkamp (2005)	9	23±2	22±4		0.5	0.63	5/9	No	
Curro (2014)	40	25.8±0.5	Not report				17/40	No	
Wen (2019)	120	21.13±2.66	20.5±2.72	1.78±0.67 (n=42)			95/120	Yes	Improve (n=12); not change (n=32); aggravate (n=2)
OD									
Wakelkamp (2005)	6	24±3	22±4		0.36	0.63	1/6	No	
Lv (2015)	72	19.4±1.4	13.3±0.7	6.2±1.2	-0.65±0.3	-0.25±0.22	69/72	Yes	Not change (n=23); aggravate (n=2)
Rajabi (2019)	23	25	21		0.24	0.4	18/23	No	

VA: Visual acuity.

methylprednisolone in all included studies was approximately from 6 to 8 g, less than 10 g. For OD group, surgical procedure included three-wall coronal decompression^[14], trans-conjunctival inferior orbitotomy approach in combination with transcaruncular medial orbitotomy^[18], endoscopic trans-ethmoidal fat decompression (ETFD)^[17].

Study characteristics are summarized in Table 1. VA was considered as main outcome in all the studies included. The baseline situation including gender, smoker number (n=66, 42.6%), history of diabetes (n=8, 5.2%), history of hyperthyroidism (n=149, 96.1%), duration of Graves' ophthalmopathy (GO; >6mo) and CAS^[20] was recorded before treatment. All included studies but one^[18] reported CAS before treatment, and all the cases were classified as active TAO (CAS score ≥3). Other recorded index included RAPD^[16,19], atypical crowding^[16], impairment of color vision^[16,19], visual field defects^[16,19], optic disc swelling^[16,18], and peripapillary retinal nerve fiber layer (PRNFL) thickness^[18]. For quality assessment, we used Jaded Scale^[21] to assess RCTs and JBI appraisal^[22] to assess case series.

The outcome data is provided in Table 2. VA was considered as main outcomes while proptosis reduction and change in diplopia were considered as second outcomes. All the included studies measured pre- and post- ocular protrusion

except for one study^[16]. Hertel exophthalmometry was used to assess ocular protrusion. The basis of exophthalmometry is the measure of the distance of the corneal apex from the level of the lateral orbital rim using an exophthalmometer^[23]. All of them demonstrated an improvement in post-treatment proptosis. Overall, weighted mean in proptosis reduction estimated at 1.64 and 5.45 mm in patients treated with ivGC and OD respectively. The estimated reduction data was obtained by weighted calculation based on data from all included studies (In ivGC group, mean reduction=1, n=9; mean reduction=1.78, n=42. In OD, mean reduction=2, n=6; mean reduction=6.2, n=72; mean reduction=4, n=23).

As restoration of VA was the primary goal in DON treatment, change in VA was evaluated in all studies. All studies demonstrated an improvement in post-treatment VA. And according to χ^2 test, the number of patients with improved VA differed significantly in ivGC and OD group (117/169 vs 88/101 patients, P=0.0009). Whereas in one study^[14], there was no significant difference in the number of patients with improved VA between the ivGC group and the surgery group (5/9 vs 1/6 patients, P=0.13).

Diplopia was discussed in two studies^[17,19]. Studies presented results regarding pre-existing and new onset diplopia. Wen and Yan^[19] found that twelve patients (20.0%) relieved from double

Table 3 Post-treatment complications

Author (y)	Hyperglycaemia	Digestive symptom	Cardiovascular symptoms	Mental symptoms	Myalgia/arthralgia	Cushing	Newly-developed diplopia	Epistaxis	Infraorbital nerve hypoesthesia	Decrease in extraocular muscle motility	<i>n</i>
IvGC (<i>n</i> =93)											
Wakelkamp (2005)	6		1			9					
Curro (2014)	1	1	3	6	2						
Wen (2019)	8	14				19					
OD (<i>n</i> =62)											
Wakelkamp (2005)									4	1	
Lv (2015)							5	10			
Rajabi (2019)						Not report					

vision after ivGC therapy while 2 (3.3%) patients' diplopia deteriorated. Lv *et al*^[17] found that 6.94% patients got new-onset diplopia immediately after surgery, however all had complete resolution of symptoms within 3mo and no cases of surgically-induced diplopia were found at the final review.

For post-treatment complication, one study^[18] did not report complication. All remaining studies presented a wide variety of minor and major intra-treatment and post-treatment complications. The results are presented in Table 3. In ivGC group, 28 patients (30.43%) showed a slight appearance of Cushing's and making it the most common complication in ivGC group. Other complications of ivGC included hyperglycaemia (*n*=15, 16.13%), digestive symptom (*n*=15, 16.13%), cardiovascular symptoms (*n*=4, 4.30%), mental symptoms (*n*=6, 6.45%) and myalgia/arthralgia (*n*=2, 2.15%). As for OD group, 10 patients (16.13%) experienced post-operative epistaxis, making it the most common complication in OD group. Other complications included newly-developed diplopia (*n*=5, 8.06%), infraorbital nerve hypoesthesia (*n*=4, 6.45%) and decrease in extraocular muscle motility (*n*=1, 1.61%). No deterioration in VA and no complications such as orbital haemorrhage, cellulitis, infraorbital nerve hypoesthesia, and cerebrospinal fluid leaks were reported in the included studies.

Although the aim of our study was to proceed to a Meta-analysis, no quantitative synthesis could be performed, due to the absence of data, key statistical measures (standard deviation) and the variable values.

DISCUSSION

This system review found that both OD surgery and intravenous high-dose steroid shock therapy were effective, safe, and feasible for DON treatment. However, certain conclusions were limited due to differences in design and intervention methods.

A myriad of different techniques and approaches have been reported for the treatment of DON^[24]. Corticosteroids play a dominant role in drug decompression, which can be

administered orally, intravenously, or locally (subconjunctival or retrobulbar injections)^[25]. Previous studies indicated that ivGC worked better than oral glucocorticoids in response rate and drug resistance^[26-28]. And the treatment of ivGC was recommended for active moderate to severe GO patients as suggested by the consensus of experts^[29]. However, more evidence should be required for the best cumulative dose and weekly medication protocol. OD could be divided into fat decompression and bone decompression. According to different operation routes, bone decompression can be divided into external (eyelid or skin), ear, skull, and nose approaches. Although internal wall decompression was conventionally considered to be the most appropriate decompression method for DON^[30], the safety and efficacy of 2-wall and 3-wall decompression have also been proved in DON treatment^[31]. This systematic review included a study of endoscopic trans-ethmoidal medial orbital wall decompression (ETMOWD)^[17], a study of coronal decompressive surgery^[14] and a study of trans-conjunctival inferior orbitotomy approach in combination with trans-caruncular medial orbitotomy^[18].

We noted that 96.1% of the included patients had hyperthyroidism and more than 40% of them had smoking history. The most common clinical features before treatment were VA decline, visual field defect, and apical crowding on CT. We divided the included studies into ivGC group and OD group to make comparison. Patients in both ivGC group and OD group were defined as active TAO (CAS \geq 3), except that one study in OD group did not report CAS score. This may lead to bias when comparing efficacy in two groups.

Both ivGC group and OD group demonstrated decrease in CAS after treatment. Furthermore, improvement in post-treatment VA was reported in both groups. According to χ^2 test, the proportion of patients with improved vision in OD group was much higher than that in ivGC group ($P<0.001$), indicating that OD might have better efficacy in improving VA among patients with DON. Furthermore, nearly 40% of patients had no response to ivGC or relapsed after

discontinuation, while similar situation was not reported in OD group. Studies have found that in patients in whom medical decompression was not able to inactivate GO within a few weeks, orbital congestion, venous stasis, and anatomic factors may play a more important role than inflammation in the pathogenesis of DON, and consequently steroids alone may not treat DON permanently^[16,32]. They suggested that the presence of disc edema and high CAS (>5) were significantly associated with unresponsiveness to steroids and should be indication for surgery^[16,32]. This may explain why OD group in this review had higher proportion of patients with improved VA.

Proptosis reduction was another important index to measure the effect of treatment. Through weighted calculation, it seemed that OD group had better effect on reducing proptosis than ivGC group. Previous studies also reported that glucocorticoids did not show better effect on relieving exophthalmos compared with placebo or non-surgical therapy^[33]. Whereas for orbital decompression, studies have pointed out that it proves effective for correcting exposure keratopathy, restoring optic nerve function as well as for disfiguring exophthalmos^[34]. Furthermore, bony OD in combination of fat decompression may provide greater access to the middle and posterior intraconal fat than traditional approaches, thus this may be responsible for the greater degree of proptosis reduction^[17,35].

Two included studies discussed diplopia before and after treatment. One study in ivGC group reported that 20.0% patients relieved from double vision after ivGC therapy^[19] while another study in OD group reported that 6.94% patients got new-onset diplopia immediately after surgery^[17]. It seemed that steroid therapy worked better in improving pre-treatment diplopia while OD therapy had the risk of post-treatment diplopia. Previous study suggested that decompression allows the bulb of the eye to recess back into the orbit, but with ocular recession the vector of pull for the extraocular muscles changed and postoperative double vision might occur^[36]. Experts also advocated that preservation of a horizontal bony strut at the junction of the medial wall and floor of the orbit (infero-medial orbital strut)^[37] and 'balanced decompression' involving removal of both medial and lateral orbital walls so as to prevent the displacement of the orbit in any direction^[38-39] may help avoid diplopia after surgery. However, since diplopia was discussed in only 2 included studies in this systematic review, more evidence should be needed before drawing the conclusion.

For post-treatment complication, ivGC group was associated with more side-effect compared with OD group. The most common complication of steroid therapy was Cushing's syndrome. Other common syndrome included hyperglycaemia, digestive symptom, cardiovascular symptoms, mental

symptoms, and myalgia/arthralgia. The incidence of major side effects of glucocorticoids has been related to the cumulative dose administered or to the presence of comorbidity^[40-41]. One study suggested that excluding patients with concurrent severe systemic diseases from steroid administration may help avoid potential severe side effects^[16]. Therefore, it is of great significance to control the cumulative dose and comprehensive consideration of the health status of the patients should be paid attention to before using glucocorticoids. Monitoring liver function, mental disorders, and other serious side effects during the process might help reduce post-treatment complication of steroid therapy^[16]. As for OD group, the most common complication was post-operative epistaxis. Only a few cases reported newly-developed diplopia, infraorbital nerve hypoesthesia and decrease in extraocular muscle motility. However, studies suggested that for patients with severe GO, the active immune attack could not be stopped by surgery and might even be stimulated because of the surgical stress^[14]. And patients with this kind of severe GO therefore did need corticosteroids as first-line therapy despite plenty of side-effects.

The results of this systematic review are liable to certain limitations. Our conclusion was based on the five included studies, only one of which was a RCT with a small sample size. We have included a series of retrospective or prospective case series with no control group leading to high risk of bias and low reliability. Additionally, besides low evidence and high risk of bias, we confronted difficulty in low sample sizes, incomplete reporting data, heterogeneity of study design, and different evaluation criteria. Furthermore, we conducted a comprehensive search with limitation of language and year of publication in several bibliographic databases, which might miss potential eligible studies.

This systematic review highlights the treatment of DON which still lacks strong evidence in guidance. So far, there are few prospective RCTs studying the treatment of DON, and the huge heterogeneity of available data makes it impossible to perform a Meta-analysis on a logarithmic scale. In view of the lack of intervention and standardization of outcome indicators, more evidence is required to understand the best strategy of DON treatment.

In conclusion, our systematic evaluation confirmed the role of ivGC and OD in the management of DON. OD seems to work better than ivGC in improving postoperative vision, relieving exophthalmos, and reducing recurrent optic neuropathy. However, more RCTs are needed to prove this conclusion.

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