



Efficacy of Periocular and Orbital Steroid Injection in Active Thyroid Eye Disease Affecting Extraocular Muscles: A Systematic Review

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ARTICLE INFO	ABSTRACT
Published Online: 29 September 2026	Introduction: Thyroid eye disease (TED) is an autoimmune inflammatory orbital disorder in which extraocular muscle involvement commonly leads to motility restriction and diplopia. Systemic corticosteroids are effective but often limited by adverse effects, prompting interest in localized steroid delivery. Objective: To systematically review the clinical outcomes of periocular and orbital steroid injection in patients with active TED and extraocular muscle involvement. Methods: A systematic search of PubMed, the Cochrane Library, and ScienceDirect was conducted in accordance with PRISMA guidelines. Studies evaluating periocular or orbital steroid injection in active TED with extraocular muscle involvement were included. Outcomes of interest were Clinical Activity Score, proptosis, extraocular muscle motility, and diplopia. Due to clinical and methodological heterogeneity, a qualitative narrative synthesis was performed. Results: Eight studies were included in the qualitative synthesis. Periocular and orbital steroid injection consistently reduced inflammatory activity across studies. Improvements in proptosis were modest and inconsistently reported. Extraocular muscle motility and diplopia outcomes were heterogeneous, with partial improvement or stabilization observed in a subset of patients, particularly those with shorter disease duration. Discussion: Local steroid injection provides effective suppression of orbital inflammation but demonstrates variable impact on structural and functional outcomes. The degree of response appears influenced by disease stage, assessment methods, and treatment protocols. Conclusion: Periocular and orbital steroid injection is a viable local treatment option for active TED with extraocular muscle involvement, offering reliable inflammation control and potential functional benefit in selected patients.
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INTRODUCTION

Thyroid eye disease (TED), also known as thyroid-associated ophthalmopathy or Graves' ophthalmopathy, is an autoimmune inflammatory disorder of the orbit and represents the most common extrathyroidal manifestation of Graves' disease.^{1,2} The prevalence of TED among patients with autoimmune thyroid disease is substantial, and although the severity varies widely, a significant proportion of affected individuals develop clinically meaningful orbital involvement. TED is associated with considerable morbidity due to its impact on visual function, facial appearance, and

overall quality of life, making it a challenging condition to manage in daily clinical practice.^{1,2}

The natural history of TED is classically described as biphasic. The initial active or inflammatory phase is characterized by progressive orbital inflammation, followed by a chronic inactive phase marked by fibrosis and residual anatomical changes.³ Therapeutic interventions are most effective during the active phase, when inflammatory processes are still potentially reversible. Once fibrosis dominates, treatment options become limited and often shift toward rehabilitative or surgical approaches. Consequently, early identification and appropriate management of active

disease are critical to preventing irreversible functional impairment.³

Extraocular muscle involvement is a defining pathological feature of active TED and a major determinant of functional disability. Autoimmune-mediated inflammation leads to infiltration of extraocular muscles by lymphocytes and fibroblasts, accompanied by accumulation of glycosaminoglycans and tissue edema.^{4,5} These changes result in muscle enlargement and stiffness, producing restrictive myopathy that manifests clinically as motility limitation, diplopia, and impaired binocular vision. Importantly, these symptoms can occur independently of marked proptosis, underscoring the central role of extraocular muscle pathology in the clinical expression of TED.^{4,5}

Diplopia and ocular motility disturbances are among the most distressing symptoms for patients with TED. Even mild or gaze-dependent diplopia can significantly disrupt daily activities such as reading, driving, and work-related tasks, leading to reduced quality of life and psychological distress.⁶ Patient-reported outcome measures have consistently demonstrated that functional visual impairment related to extraocular muscle involvement contributes disproportionately to disease burden compared with cosmetic concerns alone.⁶

Radiologic studies using computed tomography and magnetic resonance imaging have provided valuable insights into the anatomical correlates of extraocular muscle dysfunction in TED. These imaging modalities consistently demonstrate selective enlargement of extraocular muscles, most commonly affecting the inferior and medial rectus muscles during the active phase of disease.⁷ The degree of muscle enlargement correlates with clinical motility restriction and diplopia severity, supporting the use of imaging as an adjunctive tool for disease assessment and therapeutic monitoring.⁷

The primary goal of treatment in active TED is suppression of orbital inflammation in order to halt disease progression, alleviate symptoms, and prevent long-term sequelae. Systemic corticosteroids have long been established as a mainstay of therapy due to their potent anti-inflammatory effects and demonstrated efficacy in reducing disease activity and soft tissue inflammation.⁸ Randomized clinical trials have shown that systemic steroid therapy can lead to meaningful short-term improvements in inflammatory signs and symptoms in active disease.⁸

Despite their effectiveness, systemic corticosteroids are associated with a well-recognized spectrum of adverse effects. These include metabolic complications such as hyperglycemia and weight gain, cardiovascular risks, psychiatric disturbances, osteoporosis, and increased susceptibility to infection, particularly when high doses or prolonged treatment courses are required.⁹ Such risks may limit their applicability in certain patient populations and

have driven interest in alternative therapeutic approaches that maintain efficacy while reducing systemic toxicity.

Local corticosteroid administration via periocular or orbital injection has emerged as a targeted treatment strategy aimed at delivering high concentrations of anti-inflammatory medication directly to inflamed orbital tissues while minimizing systemic exposure. Peribulbar and retrobulbar injection techniques allow corticosteroids to diffuse through the retroseptal space and reach the extraocular muscles and orbital fat, which are key sites of inflammation in active TED.¹⁰ This localized approach is theoretically well suited to patients with predominant extraocular muscle involvement and motility-related symptoms.

Several clinical studies have reported favorable outcomes following periocular or orbital steroid injection, including reductions in inflammatory activity, improvements in diplopia, and decreases in extraocular muscle size on imaging.¹⁰ However, these studies vary considerably in design, patient selection, injection technique, steroid formulation, dosing regimen, and outcome assessment. As a result, the overall effectiveness and consistency of response to local steroid therapy in active TED remain difficult to interpret from individual reports alone.

Importantly, despite the clinical relevance of extraocular muscle–predominant disease, no systematic review has specifically focused on the outcomes of periocular and orbital steroid injection in patients with active TED and documented extraocular muscle involvement. Existing reviews have largely emphasized systemic therapies or have pooled heterogeneous local interventions without detailed attention to motility and diplopia outcomes. Therefore, a focused synthesis of the available evidence is needed to clarify the clinical role of periocular and orbital steroid injection in this distinct patient population.

Accordingly, this systematic review aims to comprehensively evaluate the clinical outcomes of periocular and orbital steroid injection in patients with active thyroid eye disease and extraocular muscle involvement. The review specifically examines changes in disease activity, proptosis, extraocular muscle motility, and diplopia, with the goal of providing a clearer understanding of the therapeutic potential and limitations of localized steroid therapy in the management of active TED.

METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to ensure methodological transparency and reproducibility.¹¹

Literature Search Strategy

A comprehensive literature search was performed across three electronic databases: PubMed, the Cochrane Library, and ScienceDirect. The search strategy was designed

to identify studies evaluating periocular or orbital steroid injection in patients with active thyroid eye disease or thyroid-associated ophthalmopathy. Keyword-based Boolean combinations were used to capture both historical and contemporary terminology, including variations of thyroid eye disease, local steroid injection techniques, and extraocular muscle-related outcomes. No field restrictions were applied to maximize sensitivity. The final search strategy was intentionally broad to account for variability in terminology and study design across different publication eras. All databases were searched from inception to the most recent update prior to manuscript preparation.

Eligibility Criteria

Studies were considered eligible if they met the following criteria. The population consisted of patients diagnosed with active thyroid eye disease or thyroid-associated ophthalmopathy, with documented extraocular muscle involvement. Extraocular muscle involvement was defined by clinical motility restriction, diplopia, abnormal Hess chart findings, or radiologic evidence of muscle enlargement. The intervention of interest was periocular or orbital corticosteroid injection, including peribulbar, retrobulbar, intraconal, or deep orbital approaches. Eligible comparators included baseline pre-treatment assessments or non-injection management strategies. Studies were required to report at least one of the following outcomes: Clinical Activity Score, proptosis, extraocular muscle motility, or diplopia. Both prospective and retrospective clinical studies were included.

Exclusion criteria comprised studies involving inactive or fibrotic disease, systemic corticosteroid therapy without a local injection component, surgical or radiotherapy-based interventions without periocular or orbital steroid injection, case reports, review articles, conference abstracts without full text, and non-English publications.

Study Selection

All retrieved records were screened independently at the title and abstract level to assess potential relevance. Full-text articles were subsequently reviewed for eligibility based on the predefined inclusion and exclusion criteria. Discrepancies during study selection were resolved through discussion and consensus. The study selection process,

including reasons for exclusion at each stage, is summarized in the PRISMA flow diagram (Figure 1).

Data Extraction

Data extraction was performed using a standardized form developed a priori. Extracted variables included first author and year of publication, country, study design, population characteristics, criteria used to define active disease, methods used to assess extraocular muscle involvement, details of the injection protocol, comparator, duration of follow-up, and reported outcomes. Outcomes of interest included changes in Clinical Activity Score, proptosis, extraocular muscle motility, and diplopia. When outcomes were reported using different metrics, results were extracted as reported without transformation. All extracted data were compiled into a single “Characteristics and Results of Included Studies” table.

Risk of Bias Assessment

Risk of bias was assessed at the study level using a domain-based qualitative approach appropriate for non-randomized and single-arm clinical studies. Factors considered included study design, patient selection, outcome assessment methods, completeness of follow-up, and clarity of intervention reporting. Randomized or controlled studies were assessed for allocation procedures and baseline comparability. Each study was categorized as having low, moderate, or high risk of bias based on overall methodological quality and reporting transparency. The risk-of-bias assessment was incorporated into the final characteristics table.

Data Synthesis

Due to substantial clinical and methodological heterogeneity across the included studies, quantitative synthesis was not performed. Sources of heterogeneity included differences in study design, steroid type and dosage, injection technique, frequency of administration, follow-up duration, and outcome definitions, particularly for extraocular muscle motility and diplopia. Therefore, a qualitative narrative synthesis was conducted to summarize and contextualize the findings across studies. Outcomes were synthesized descriptively according to disease activity, proptosis, extraocular muscle motility, and diplopia.

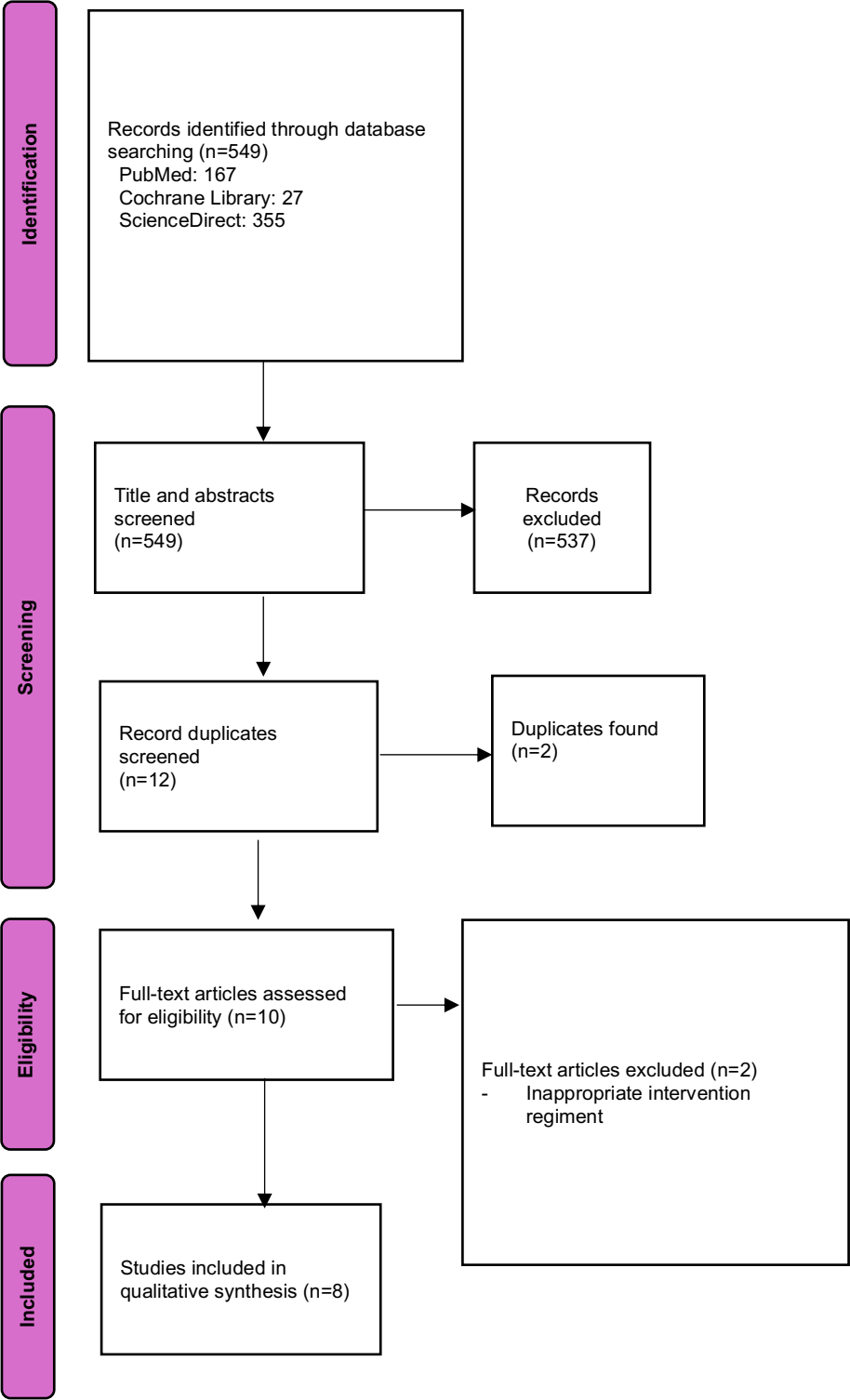


Figure 1. Diagram flow of literature search strategy for this systematic review

Table 1. Study Characteristics and Reported Outcomes of Periocular and Orbital Steroid Injection in Patients With Active Thyroid Eye Disease and Extraocular Muscle Involvement

First Author (Year)	Country	Study Design	Population Characteristics	Disease Criteria (Active TED)	Activity (Active TED)	Extraocular Muscle Involvement Definition	Intervention (Type, Steroid, Dose, Frequency)	Comparator	Follow-up Duration	CAS Outcome	Proptosis Outcome	EOM Outcome	Motility	Diplopia Outcome	Summary of Findings	Risk of Bias
Swaify (2023)	Egypt	Prospective, double-masked, randomized clinical trial (paired-eye design)	18 patients (36 orbits) with bilateral active, moderate-to-severe TED; mean age 40.2±10 years; disease duration <6 months	Active defined using EUGOGO criteria; mean baseline CAS ≈5 in both arms	TED using mean CAS ≈5	EOM involvement assessed clinically; baseline EOM involvement present in 72.2% of orbits in both groups	Periocular injections: Methotrexate 7.5 mg (0.3 mL) ×3 injections at weeks 0, 3, and 6 vsTriamcinolone acetonide 20 mg (0.5 mL) ×3 injections at weeks 0, 3, and 6	Contralateral eye treated with alternative injection (within-patient comparison)	6 months (24 weeks post-treatment; total study duration 30 weeks)	Significant reduction in both groups: MTX 5.2±0.89 → 0.9±1.7; TA 5.1±0.9 → 1.0±1.7 (both p<0.001); no between-group difference	Significant reduction in both groups: MTX −1.33±1.94 mm (p=0.01); TA −1.0±2.0 mm (p=0.049); ≥2 mm reduction in 33.3% (MTX) vs 44.4% (TA)	Minimal response; improvement in monocular ductions ≥8° observed in only 5.6% of orbits in each group		Not specifically quantified; diplopia evaluated indirectly through EOM ductions and motility response	Periocular methotrexate and triamcinolone were both effective in reducing inflammatory activity (CAS) and soft tissue signs in active TED, with modest proptosis improvement and minimal effect on EOM motility; safety profile was favorable with no serious complications	Low–moderate risk: randomized, double-masked design strengthens internal validity; limitations include small sample size, paired-eye design, and short follow-up for late complications
Yamana (2024)	Japan	Prospective single-arm clinical study	28 patients (56 eyes); 23 women, 5 men; mean age 38.7±11.1 years	Active defined as CAS ≥3	TED	Localized inflammation of extraocular muscles confirmed clinically and by MRI; inclusion required EOM inflammation	Deep orbital steroid injection: Triamcinolone acetonide 40 mg (1 mL of 40 mg/mL), single bilateral injection delivered posterior to the orbital septum at medial and lateral aspects of upper and lower eyelids	Baseline (pre-injection)	4 weeks	Mean CAS decreased from 4.22±1.29 to 2.20±1.10 at 4 weeks (p<0.001)	No significant change in exophthalmos measured by MRI (20.0±3.2 mm to 19.0±3.2 mm; p=0.299)	Ocular motility improved: HAR% increased from 94.42±4.45% to 98.94±6.26% (p=0.014); MRI showed reduction in EOM cross-sectional area (21.1–36.2% depending on muscle)		Diplopia not directly quantified; motility assessed using HAR% as a surrogate	A single deep orbital triamcinolone injection significantly reduced inflammatory activity (CAS), improved eyelid retraction and ocular motility, and decreased EOM size on MRI, with no significant effect on proptosis and no serious ocular or systemic adverse effects	Moderate risk: prospective design with objective imaging outcomes, but single-arm study without control group and short follow-up
Eid (2024)	United States	Retrospective single-center study	15 patients; mean age 59.2 ± 13.0 years; 89% female; 33 orbital injections analyzed	Active baseline CAS 3.84	TED; mean	EOM assessed clinically as part of routine exam; motility changes categorized as improved/stable/worsened	Orbital steroid injections: triamcinolone acetonide 40 mg/mL mixed 1:1 with dexamethasone 4 mg/mL; 0.5–1.0 mL per injection; inferolateral intraconal approach; mean 1.31 injections per orbit (range 1–3)	Baseline (pre-injection)	~1 month (mean 4 weeks)	Mean CAS decreased from 3.84 to 3.00 (Δ −0.84; p = 0.0004)	No significant change in Hertel exophthalmometry (21.7 ± 9.4 mm vs 21.8 ± 7.6 mm; p = 0.56)	21% improved, 72% stable, 7% worsened; no statistically significant overall change (p = 0.50)		Subjective diplopia not separately quantified; subjective orbital pain/pressure improved in 67% of patients	Orbital injections of combined triamcinolone and dexamethasone significantly reduced inflammatory activity (CAS) and subjective orbital pain/pressure, with no significant effect on proptosis or EOM motility and no steroid-induced IOP rise or major complications	Moderate risk: retrospective design, small sample size, no control group, short follow-up

Wang (2020)	China	Retrospective cohort study	386 patients (515 eyes); mean age 45.1 ± 12.8 years; 62.2% female; mild–severe TAO included	Active TAO defined as CAS ≥3 at baseline	EOM involvement defined as limited eye motility (≥5° reduction in any direction) assessed using Hess chart	Peribulbar corticosteroid injection: triamcinolone acetonide 40 mg + dexamethasone 2.5 mg per session; injected into supra- and infra-orbital regions; repeated every 4 weeks (monthly); ≥2 injections, typically 3–4 until no further improvement	Baseline (pre-injection)	≥6 months (monthly for first 6 months, then quarterly)	Higher CAS associated with better therapeutic effectiveness; CAS significantly improved overall (exact mean change not uniformly reported)	Proptosis improved in 49/118 cases (41.52%); reduction ≥2 mm used as effectiveness criterion	Eye motility disturbance improved in 29/96 cases (30.21%) based on Hess chart assessment	Diplopia alleviated to varying degrees; improvement incorporated within eye motility outcomes	Peribulbar injection of combined triamcinolone and dexamethasone was effective in improving inflammatory activity, eyelid signs, proptosis, and EOM dysfunction in active TAO, particularly in mild–moderate disease; therapeutic response was influenced by gender, smoking status, thyroid function, disease severity, and CAS	Moderate risk: large sample size and structured outcomes, but retrospective design, no control group, heterogeneous disease severity
Poonyathalang (2005)	Thailand	Prospective non-comparative pilot study	19 patients (27 eyes); mean age 39.4 years (range 20–53); 9 males, 10 females; unilateral or bilateral TAO	Active TAO assessed clinically (NOSPEC signs); patients with proptosis and diplopia due to limited EOM; CT-confirmed EOM enlargement	Limited EOM function with abnormal Hess test; EOM enlargement on CT	Retrobulbar triamcinolone acetonide 40 mg (1 mL) per eye; weekly injections for 4 weeks (total 4 injections/orbit)	Baseline (pre-injection)	6–16 months (mean ~12 months); primary assessments at 3 and 6 months	Not reported as CAS (pre-CAS era); activity inferred from clinical signs	Improvement ≥1 mm in 15/27 eyes (56%) at 3 months; mean reduction ~1.7 mm; effects largely maintained at 6 months	Improved in 7/17 patients (41%); no change in 8 (47%); worsened in 2 (12%); stable at 6 months	Improvement reported subjectively in association with EOM improvement; not quantified separately	Retrobulbar triamcinolone improved proptosis and EOM function in a substantial proportion of patients with TAO, with generally stable visual function and durability to 6 months; IOP elevation occurred in some eyes but was mostly medically manageable	Moderate risk: small sample, non-comparative design, no standardized CAS, potential measurement variability
Bagheri (2020)	Iran	Prospective non-comparative case series	17 patients (31 eyes); mean age 49.8 ± 12.2 years; 64.7% male; all had prior systemic steroid resistance, dependence, or steroid-related complications	Active TED defined as CAS ≥3; NOSPECS severity score ≥3; no compressive optic neuropathy	EOM involvement assessed by duction limitation and presence of strabismus; motility quantified clinically	Intraorbital retroseptal steroid injection: triamcinolone acetonide 20 mg + dexamethasone 4 mg per site; injected into superior and inferior retroseptal orbital spaces; 3–4 injections at 1-month intervals	Baseline (pre-injection)	Minimum 3 months after last injection (total treatment period ~3–4 months)	Mean CAS improved from 5.2 ± 1.3 to 1.6 ± 1 at final follow-up (p < 0.001)	Mean exophthalmos reduced by 1.2 ± 1.1 mm; ≥2 mm reduction in 22.6% of eyes	Improvement mainly in supraduction (−0.4 to −0.2; p = 0.04); other ductions largely unchanged	Strabismus resolved completely in 1 of 5 affected patients; overall deviation angles largely unchanged	Intraorbital steroid injections markedly reduced inflammatory activity (CAS), improved lid retraction and modestly improved proptosis and selected EOM movements in active TED patients unsuitable for systemic steroids, with acceptable short-term safety	Moderate risk: single-arm design, small sample size, no control group
Bordaberry (2009)	Brazil	Prospective pilot case series	21 patients (42 eyes); mean age 50 ± 13.4 years; 17 female; moderate (n=11) and	Active GO defined as modified CAS ≥4 (9-point scale)	EOM involvement evidenced by diplopia, motility impairment, and CT-impairment	Peribulbar triamcinolone acetonide 20 mg per injection; four injections per orbit at 2-week intervals	Baseline (pre-injection)	Mean ≥14 months; primary	Mean CAS decreased from 6.38 ± 1.49 to 1.8 ± 1.12 at 6 months	≥2 mm reduction in exophthalmos observed in 38% of patients	Motility score improved (mean reduction 0.95 ± 0.74 points; p=0.01);	Diplopia improved by ≥1 grade in 65% of patients	Repeated triamcinolone significantly reduced inflammatory	Moderate risk: uncontrolled design, small sample, modified CAS;

			severe GO with optic neuropathy (n=10)		documented enlargement	muscle (inferolateral and superomedial quadrants)		outcomes at 6 months	(p=0.01); ≥2-point CAS reduction in 95%		improved function clinically	EOM noted	improved motility, proptosis, and diplopia in moderate–severe GO; 66% of eyes with optic neuropathy resolved with injections alone; transient IOP elevation occurred in a minority	strengths include prospective follow-up and standardized assessments
Ebner (2004)	Argentina (multicentre)	Multicentre prospective pilot study with randomized control group	41 patients (efficacy population); TAO duration ≤6 months; both sexes; endocrine status variable	Early active TAO defined by recent onset with diplopia; CAS not explicitly used as inclusion criterion	Presence of diplopia; EOM enlargement quantified by CT (muscle diameter normalized to optic nerve size)	Periocular (peribulbar) triamcinolone acetonide 20 mg per orbit (40 mg/mL); injected into inferolateral quadrant; weekly ×4 injections	No-treatment control group	6 months (assessments at weeks 10 and 24)	CAS not reported	No significant change in exophthalmometry between groups	Significant reduction in EOM size on CT, especially superior rectus–levator complex (p=0.006); overall reduction across recti compared with control	Significant increase in binocular single-vision area (Goldmann perimeter) in treatment group vs control at weeks 10 and 24 (p<0.01)	Periocular triamcinolone significantly reduced diplopia and extraocular muscle size in early active TAO without systemic or ocular adverse effects; visual acuity, IOP, and systemic parameters remained stable	Low–moderate risk: prospective design with control group and objective outcomes; limitations include pilot size and baseline imbalance in motility severity

RESULTS

Study Selection

The systematic search across PubMed, the Cochrane Library, and ScienceDirect identified 549 records, reflecting a broad body of literature related to thyroid eye disease and corticosteroid therapy. Following initial screening of titles and abstracts, the majority of records were excluded because they addressed systemic corticosteroid therapy, radiotherapy, surgical interventions, inactive disease phases, or populations without documented extraocular muscle involvement. After this stage, only a small subset of potentially relevant studies remained, highlighting the relative scarcity of literature specifically evaluating periocular or orbital steroid injection for extraocular muscle–predominant active disease.

Duplicate screening identified two overlapping records, leaving ten unique full-text articles for eligibility assessment. Full-text review led to the exclusion of two studies due to the use of inappropriate intervention regimens that did not meet the predefined criteria for local periocular or orbital steroid injection. Ultimately, eight studies met all inclusion criteria and were incorporated into the qualitative synthesis. The study selection process and reasons for exclusion at each stage are summarized in Figure 1, illustrating a highly selective filtering process driven by strict adherence to the predefined PICO framework.

Characteristics of Included Studies

The eight included studies, published between 2004 and 2024, collectively evaluated patients with active thyroid eye disease or thyroid-associated ophthalmopathy characterized by extraocular muscle involvement. Study designs were diverse and included one randomized controlled pilot study with a non-treatment control group, several prospective and retrospective single-arm investigations, and observational cohort studies. Sample sizes varied substantially, ranging from small pilot cohorts to large retrospective series, reflecting differences in study scope and institutional experience.

Definitions of active disease evolved over time, with earlier studies relying on clinical descriptors of inflammatory activity and more recent investigations applying standardized Clinical Activity Score thresholds. Despite these differences, all studies focused on patients in the inflammatory phase of the disease rather than fibrotic or inactive stages. Extraocular muscle involvement was consistently required but assessed using heterogeneous methods, including clinical motility limitation, diplopia assessment, Hess chart analysis, and imaging-based measurement of muscle enlargement using CT or MRI.

Intervention protocols demonstrated marked variability. Periocular approaches included peribulbar and retrobulbar injections, while some studies employed deeper orbital or intraconal injection techniques. Triamcinolone

acetate was the most frequently administered corticosteroid, either as monotherapy or combined with dexamethasone, with doses typically ranging between 20 and 40 mg per injection. Treatment schedules varied from a single injection to repeated weekly or monthly injections over several weeks. Follow-up duration ranged from short-term assessments at four weeks to longer-term observation exceeding one year, contributing to heterogeneity in outcome reporting.

Clinical Activity Score Outcomes

Reduction in inflammatory activity, as reflected by changes in Clinical Activity Score, emerged as the most consistent outcome across the included studies. In investigations that formally applied CAS, periocular or orbital steroid injection resulted in rapid and clinically meaningful reductions in disease activity. Improvements were often evident within weeks of treatment initiation and persisted throughout follow-up periods, indicating sustained anti-inflammatory effects of localized corticosteroid delivery.

Several studies demonstrated a shift from moderate-to-severe active disease to low-activity states following treatment, suggesting that periocular and orbital steroid injections effectively suppress orbital inflammation in selected patients. In earlier studies conducted prior to widespread adoption of CAS, clinical improvement was inferred from reductions in inflammatory signs and symptoms, including orbital pain, swelling, and erythema. Collectively, these findings indicate a consistent therapeutic effect of local steroid injection on inflammatory activity in active thyroid eye disease with extraocular muscle involvement.

Proptosis Outcomes

Changes in proptosis following periocular or orbital steroid injection were less pronounced and more variable than improvements in inflammatory activity. Some studies reported modest reductions in exophthalmometry measurements, generally in the range of 1–2 mm, with a subset of patients achieving clinically meaningful improvement. These reductions were more frequently observed in studies employing repeated injection protocols or longer follow-up durations.

Conversely, several investigations reported no statistically significant change in proptosis, particularly in studies with short follow-up periods or single-injection regimens. Imaging-based assessments similarly demonstrated limited reductions in globe protrusion despite measurable decreases in extraocular muscle size. Overall, the qualitative synthesis suggests that while local steroid injection may contribute to slight improvements in proptosis, its primary benefit lies in inflammation control rather than substantial reduction of orbital protrusion.

Extraocular Muscle Motility Outcomes

Outcomes related to extraocular muscle function exhibited considerable heterogeneity across studies, reflecting differences in assessment tools, disease severity, and treatment protocols. Functional improvement in ocular motility was reported in a proportion of patients, particularly those with recent-onset disease and non-fixed motility restriction. Improvements were documented using various measures, including duction angles, Hess chart analysis, and expansion of binocular single-vision fields.

Radiologic assessments provided complementary evidence of treatment effect, with several studies demonstrating reductions in extraocular muscle thickness following periocular or orbital steroid injection. These structural changes were most consistently observed in the inferior and superior rectus muscle groups. However, functional recovery was often incomplete, and many patients experienced stabilization rather than full normalization of extraocular muscle movement. These findings suggest that local steroid therapy may mitigate inflammatory muscle enlargement and prevent progression of motility impairment, but its ability to reverse established dysfunction is limited.

Diplopia Outcomes

Diplopia outcomes were reported using both subjective patient-reported measures and objective functional assessments. Studies employing Goldmann perimetry or binocular single-vision field analysis demonstrated significant expansion of diplopia-free visual fields following treatment, particularly in patients with gaze-dependent or intermittent diplopia. Subjective improvement in diplopia severity was commonly noted, with patients reporting reduced frequency or intensity of double vision during daily activities.

Nevertheless, complete resolution of diplopia was relatively uncommon, especially in patients with long-standing disease or marked motility restriction. Several studies noted stabilization of diplopia rather than full recovery, indicating that while periocular and orbital steroid injection can improve functional vision, residual diplopia may persist due to structural or fibrotic changes within the extraocular muscles.

Heterogeneity of Included Studies

Marked clinical and methodological heterogeneity was evident across the included studies. Differences in study design, patient selection criteria, definitions of active disease, injection techniques, steroid formulations, dosing regimens, and follow-up duration contributed to variability in reported outcomes. Outcome assessment methods also varied widely, particularly for extraocular muscle function and diplopia, limiting direct comparison between studies.

Additionally, the inclusion of studies spanning two decades introduced variability related to evolving diagnostic

criteria and outcome measures. This heterogeneity precluded meaningful quantitative pooling of results. Consequently, a narrative synthesis was deemed the most appropriate approach to summarize the evidence, allowing for contextual interpretation of findings within the limitations of the available data.

DISCUSSION

Principal Findings

This systematic review provides a comprehensive qualitative synthesis of the available evidence on periocular and orbital steroid injection in patients with active thyroid eye disease characterized by extraocular muscle involvement. Across heterogeneous study designs and treatment protocols, a consistent reduction in inflammatory activity was observed following local steroid administration. Improvements in Clinical Activity Score or equivalent clinical indicators were reported in nearly all included studies, underscoring the robust anti-inflammatory effect of localized corticosteroid therapy during the active phase of disease. This finding reinforces the concept that direct orbital delivery of steroids can effectively suppress active inflammation in thyroid eye disease.

In contrast, outcomes related to proptosis, extraocular muscle motility, and diplopia were more variable and less predictable. While some patients experienced modest improvements in globe protrusion and functional motility, others showed stabilization without significant reversal of established deficits. These findings highlight an important distinction between inflammation-driven manifestations, which appear highly responsive to local steroid therapy, and structural or functional sequelae, which may be only partially reversible even during the active disease phase.

Comparison With Existing Evidence

Systemic corticosteroids have long been regarded as first-line therapy for active thyroid eye disease due to their proven efficacy in reducing inflammatory signs and symptoms.^{8,9} Randomized trials have demonstrated meaningful short-term improvements in disease activity following systemic steroid administration, forming the foundation of current guideline recommendations.¹² However, systemic therapy is frequently limited by dose-related adverse effects, leading to treatment discontinuation or suboptimal dosing in real-world practice.⁹

In this context, periocular and orbital steroid injection represents a localized therapeutic strategy that aligns with evolving trends toward individualized, organ-targeted treatment. Prior narrative reviews and guideline documents have acknowledged the potential role of local steroid injection, particularly in patients with mild-to-moderate disease or contraindications to systemic therapy.^{12,13} The present review extends these observations by systematically

synthesizing data from studies specifically focusing on extraocular muscle involvement, an aspect that has been underrepresented in broader reviews.

Importantly, the findings of this review suggest that the magnitude of inflammatory suppression achieved with local steroid injection may be comparable to that observed with systemic therapy in selected patients. However, unlike systemic steroids, which exert diffuse immunosuppressive effects, local injection concentrates therapeutic activity within the orbit, potentially reducing systemic toxicity while preserving clinical efficacy.

Interpretation of Extraocular Muscle and Diplopia Outcomes

Extraocular muscle-related outcomes emerged as a key area of heterogeneity across studies. Functional improvements in motility were observed in a subset of patients, often accompanied by radiologic evidence of reduced muscle thickness. Imaging-based outcomes provided objective confirmation that local steroid injection can reduce extraocular muscle edema and inflammation, particularly in commonly affected muscles such as the inferior and superior rectus.⁷

Nevertheless, complete restoration of normal motility was uncommon. This observation is consistent with the known pathophysiology of thyroid eye disease, in which early inflammatory changes coexist with evolving fibrotic remodeling.^{4,5} Even during the active phase, the degree of fibrosis may vary between patients and muscle groups, limiting the potential for full functional recovery. As a result, local steroid injection may be more effective in halting progression and improving partial motility deficits than in reversing advanced restrictive myopathy.

Diplopia outcomes followed a similar pattern. Patients with intermittent, gaze-dependent, or recently developed diplopia were more likely to experience improvement following treatment, whereas those with constant diplopia often demonstrated stabilization rather than resolution. This distinction supports the notion that diplopia in thyroid eye disease represents a continuum of inflammatory and mechanical components, with local steroid therapy primarily targeting the inflammatory aspect.¹⁴

Pathophysiological Considerations and Mechanisms

The therapeutic effects of periocular and orbital steroid injection are likely mediated through direct suppression of inflammatory pathways within orbital tissues. Corticosteroids inhibit lymphocyte activation, cytokine release, and glycosaminoglycan synthesis by orbital fibroblasts, leading to reduced tissue edema and cellular infiltration.^{5,15} Local delivery allows high tissue concentrations to be achieved in proximity to inflamed extraocular muscles, potentially enhancing therapeutic efficacy compared with systemic administration.

However, once fibrosis becomes established, corticosteroids are inherently limited in their ability to reverse structural remodeling. This pathophysiological constraint likely explains why improvements in inflammatory activity are consistently observed, whereas motility and diplopia outcomes remain variable. These mechanisms underscore the importance of early intervention during the inflammatory phase, when tissue changes are still potentially reversible.

Clinical Implications

From a clinical standpoint, the findings of this review support the role of periocular and orbital steroid injection as a valuable therapeutic option in selected patients with active thyroid eye disease and predominant extraocular muscle involvement. This approach may be particularly beneficial for patients who are unable to tolerate systemic corticosteroids or who present with moderate disease severity primarily affecting motility and binocular vision.

Local steroid injection may also serve as an intermediate or adjunctive therapy, bridging the gap between observation and more aggressive systemic or biologic treatments. In the context of emerging targeted therapies such as teprotumumab, which have demonstrated substantial efficacy but are associated with high cost and limited accessibility,¹⁶ periocular and orbital steroid injection may represent a pragmatic and cost-effective option in certain clinical settings.

Nevertheless, careful patient selection remains essential. Clinicians should counsel patients that while inflammation control is a reliable outcome, improvements in proptosis and diplopia are less predictable and may be incomplete. Setting realistic expectations is crucial to optimizing patient satisfaction and treatment adherence.

Limitations of the Evidence

Several limitations inherent to the available evidence must be acknowledged. Most included studies were observational in nature, with small sample sizes and limited use of control groups. Definitions of active disease and extraocular muscle involvement varied, particularly across studies spanning multiple decades. Outcome measures for motility and diplopia were heterogeneous, ranging from subjective clinical assessments to objective imaging and perimetric analyses, limiting comparability across studies.

Additionally, follow-up durations were often short, restricting evaluation of long-term efficacy and durability of response. Potential publication bias cannot be excluded, as studies reporting favorable outcomes may be more likely to be published. These limitations collectively preclude quantitative synthesis and highlight the need for cautious interpretation of the findings.

Future Research Directions

Future investigations should prioritize prospective, controlled studies with standardized definitions of disease activity and extraocular muscle involvement. Harmonization of outcome measures for motility and diplopia would facilitate comparison across studies and enable meta-analytic approaches. Comparative studies evaluating local steroid injection against systemic corticosteroids or newer biologic agents would further clarify its relative efficacy and optimal positioning within treatment algorithms.

Longer-term follow-up studies are also needed to assess durability of response and to determine whether early local steroid intervention can modify the natural course of extraocular muscle dysfunction and reduce the need for subsequent surgical correction.

CONCLUSION

Periocular and orbital steroid injection appears to be an effective local therapeutic option for patients with active thyroid eye disease with extraocular muscle involvement, particularly in reducing inflammatory activity. While consistent improvement in disease activity was observed across studies, the effects on proptosis, extraocular muscle motility, and diplopia were variable and often modest. These findings suggest that local steroid injection is most beneficial during the active inflammatory phase and may help stabilize or partially improve functional impairment rather than fully reverse established motility deficits. Given its favorable safety profile and targeted mechanism, periocular and orbital steroid injection may serve as a valuable alternative or adjunct to systemic therapy in selected patients. However, further well-designed prospective studies with standardized outcome measures are required to better define its optimal role in the management of thyroid eye disease.

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