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Local experience of concurrent three-weekly high-dose pulsed intravenous methylprednisolone and orbital radiotherapy in thyroid eye disease

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Abstract

Purpose: To analyse the outcomes of concurrent high-dose pulsed intravenous methylprednisolone (IVMP) administered every 3 weeks for 4 cycles along with orbital radiotherapy (OR) in thyroid eye disease (TED).
Study design: Retrospective case series.
Methods: The medical records of 5 patients with moderate-to-severe active TED who underwent concurrent IVMP and OR in 2022 and 2023 were reviewed. All patients received concurrent pulsed IVMP (1 g per day for 3 consecutive days, administered three-weekly for four cycles) and OR (20 Gy in 10 fractions). Improvement was assessed using the Clinical Activity Score (CAS) and International Thyroid Eye Disease (ITEDS) – Vision/Inflammation/Strabismus/Appearance (VISA) scoring system.
Results: The mean age of the 5 patients was 50.2 ± 5.2 years. The mean duration of ophthalmopathy and thyroid disease were 6.2 ± 4.2 months and 9.60 ± 9.29 months, respectively. Following treatment, there was a significant reduction in the mean CAS by 2.8 ± 1.3 ($p = 0.009$) and ITEDS-VISA scores by 5.8 ± 2.5 ($p = 0.006$). Improvement in proptosis measured by exophthalmometer was 2.3 ± 1.5 mm ($p = 0.028$). The mean follow-up duration was 6.0 ± 5.9 months.

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Conclusion: Concurrent high-dose three-weekly pulsed IVMP with OR is a safe and effective treatment modality in the management of active TED.

Keywords: corticosteroids, Graves' ophthalmopathy, orbital radiotherapy, thyroid eye disease

Pengalaman tempatan pemberian intravena methylprednisolone yang berdos tinggi setiap tiga minggu bersama radioterapi orbital secara serentak dalam penyakit mata tiroid

Abstrak

Tujuan: Untuk menganalisis hasil daripada dos tinggi Intravena Methylprednisolone (IVMP) yang diberikan secara serentak pada setiap 3 minggu selama 4 kitaran bersama radioterapi orbital (OR) dalam penyakit mata tiroid.
Reka bentuk kajian: Siri kes retrospektif.
Kaedah: Rekod perubatan 5 pesakit dengan TED aktif tahap sederhana hingga teruk yang menjalani rawatan IVMP dan OR serentak pada tahun 2022 dan 2023 telah dikaji. Semua pesakit menerima denyutan IVMP (1 g sehari selama 3 hari berturut-turut, diberikan setiap tiga minggu selama empat kitaran) dan OR (20 Gy dalam 10 pecahan) secara serentak. Penambahbaikan dinilai menggunakan Skor Aktiviti Klinikal (CAS) dan system skor Penyakit Mata Tiroid Antarabangsa (ITEDS) – Penglihatan/Radang/Strabismus/Penampilan (VISA).
Keputusan: Purata usia 5 pesakit ialah 50.2 ± 5.2 tahun. Purata tempoh oftalmopati dan penyakit tiroid adalah 6.2 ± 4.2 bulan dan 9.60 ± 9.29 bulan, masing-masing. Selepas rawatan, terdapat pengurangan yang signifikan dalam purata CAS sebanyak 2.8 ± 1.3 (p=0.009) dan skor ITEDS-VISA sebanyak 5.8 ± 2.5 (p = 0.006). Penambahbaikan dalam proptosis yang diukur menggunakan exophthalmometer ialah 2.3 ± 1.5 mm (p = 0.028). Purata tempoh susulan ialah 6.0 ± 5.9 bulan.
Kesimpulan: Gabungan pemberian dos tinggi intravena methylprednisolone dengan radioterapi orbital adalah kaedah rawatan yang selamat dan berkesan dalam pengurusan penyakit mata tiroid aktif.

Kata kunci: kortikosteroid, oftalmopati Graves, penyakit mata tiroid, radioterapi orbital

Introduction

Thyroid eye disease (TED), also known as Graves' orbitopathy or thyroid associated ophthalmopathy, is an autoimmune condition characterised by inflammation and fibrosis of the orbital tissues.[1] It can manifest in patients who are hyperthyroid, hypothyroid, or euthyroid.[2] Euthyroidism is defined as normal serum thyroid-stimulating hormone, free thyroxine, and free triiodothyronine levels within the reference ranges. TED imposes significant morbidity primarily due to its impact on visual function and cosmetic appearance.[1] The prevalence of TED varies geographically, with rates of 0.25% observed in Western populations,[3] while a Malaysian study reported a prevalence of 34.7% in patients with Graves' disease.[4]

Despite advances in understanding its pathophysiology, managing severe TED remains challenging. Traditional therapeutic modalities for severe TED include corticosteroids, orbital radiotherapy (OR), and surgical decompression.[2] However, the optimal management of severe TED continues to evolve. An emerging approach involves the concurrent administration of high-dose, pulsed intravenous methylprednisolone (IVMP) alongside OR.[5] Corticosteroids like IVMP mitigate orbital inflammation and reduce oedema, whereas OR suppresses lymphocyte infiltration into the orbital tissues.[6] Research indicates that concurrent IVMP (administered at 15 mg/kg for 4 cycles followed by 7.5 mg/kg for 4 cycles) and OR resulted in a greater reduction in Clinical Activity Score (CAS) compared to oral prednisone combined with OR.[7]

At our centre, we have adopted a regimen involving high-dose pulsed IVMP, administered at 1 g IVMP per day for 3 days, every 3 weeks, for 4 to 6 cycles depending on the clinical response. Since 2022, we have introduced a combination therapy involving high-dose pulsed IVMP with OR, anticipating synergistic therapeutic effects. The aim of this study was to conduct a retrospective evaluation of our experience with this therapeutic regimen, elucidating its effectiveness and safety profile in managing active TED.

Methods

This was a retrospective case series analysis conducted in a tertiary hospital in Kuala Lumpur, Malaysia. Patients older than 18 years old with moderate to severe active TED who underwent concurrent pulsed IVMP and OR in 2022 and 2023 were included in this study. Patients with active infection, uncontrolled hypertension and/or diabetes mellitus, liver dysfunction, a history of previous treatment for TED, or a follow-up period of less than 3 months were excluded from this study. The baseline characteristics and clinical parameters were retrospectively collected from the medical records.

The CAS[8] and International Thyroid Eye Disease-Vision/Inflammation/Strabismus/Appearance (ITEDS-VISA) scoring system[9] was used to assess the disease activity in all patients who attended the oculoplastic clinic in the eye centre. The disease activity and severity were graded at the end of each visit. An active disease was defined by a CAS score ≥ 3, and the decision to initiate treatment was made by an oculoplastic surgeon. The pulsed IVMP protocol was 1 g IVMP per day for 3 days, every 3 weeks, for 4 cycles. Pre-steroid work-up included a full blood count, renal profile, liver function test, infective screening for hepatitis and syphilis, tuberculin skin test (Mantoux), urinalysis, electrocardiogram, and chest X-ray. IVMP was contraindicated in the presence of active hepatitis, hepatic dysfunction, severe hypertension, uncontrolled diabetes mellitus, cardiovascular morbidity, or active infections.[7] If there was no contraindication, IVMP was administered under close monitoring by trained nurses with a trained medical doctor on standby for medical alerts. Prior to the initiation of each cycle, clinical (CAS and ITEDS-VISA) and laboratory (full blood count, renal profile, liver function test, and urinalysis) reviews were performed. All patients underwent computerised tomography (CT) or magnetic resonance imaging (MRI) imaging during the treatment period before initiation of OR. The patients were co-managed with the radiation oncology team in the hospital for OR. A total dose of 20 Gy in 10 fractions over 2 weeks was administered to all patients after the first cycle of IVMP. The patients were followed up for at least 3 months after the intervention. The clinical response was retrospectively evaluated from the medical records at the latest follow-up visit to the eye clinic.

Our primary outcomes were changes in CAS and ITEDS-VISA index. Secondary outcomes included changes in the degree of proptosis, best-corrected visual acuity (BCVA), the status of diplopia, and any adverse event.

Continuous variables were expressed as means and standard deviations and compared using Student t-tests. A *p*-value of less than 0.05 was considered as statistically significant. All statistical analyses were performed using the Statistical Package for Social Science (SPSS) version 29.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 5 patients were included in this study. A summary of the patients' characteristics is shown in Table 1. The mean age of the patients was 50.2 ± 5.2 years, with 3 male patients and 2 smokers. All our patients were hyperthyroid, and 2 of them achieved euthyroid status at intervention. The mean duration of ophthalmopathy was 6.2 ± 4.2 months and the mean duration of thyroid disease was 9.60 ± 9.29 months. Two of the patients (Patients 3 and 4) were diagnosed with dysthyroid optic neuropathy on presentation. All 5 patients received 4 cycles of systemic corticosteroids (1 g IVMP per day for 3 days, every 3 weeks) and orbital irradiation (20 Gy in 10 fractions over 2 weeks).

Table 1. Clinical characteristics of patients

Case	Age	Sex	Ethnicity	Smoker	Thyroid status at intervention	Treatment for thyroid condition	Duration of TD (months)	Duration of OP (months)	Presence of optic neuropathy
1	52	Male	Chinese	Yes	Euthyroid	Carbimazole	24	2	No
2	44	Male	Malay	No	Euthyroid	Nil	1	5	No
3	57	Female	Malay	No	Hyperthyroid	Carbimazole	2	3	Yes
4	46	Female	Chinese	No	Hyperthyroid	Carbimazole	9	9	Yes
5	52	Male	Chinese	Yes	Hyperthyroid	Methimazole	12	12	No

TD: thyroid disease; OP: ophthalmopathy

Table 2. Clinical response after concurrent high-dose pulsed IVMP and OR

Case	Proptosis (Pre) (mm)	Proptosis (Post) (mm)	logMAR BCVA (Pre)	logMAR BCVA (Post)	Diplopia (Pre)	Diplopia (Post)	CAS (Pre)	CAS (Post)	VISA (Pre)	VISA (Post)
1	19	17.5	0.2	0.2	IT	IT	4	0	10	2
2	21.5	18.5	0.2	0.2	Constant	With gaze	5	1	12	3
3	18	16	0.6	0.3	Constant	Constant	4	2	10	6
4	22	21.5	0.7	0.5	None	None	4	3	8	4
5	20.5	16	0.2	0.2	With gaze	IT	4	1	10	6

Pre: pre-intervention; Post: post-intervention IT: intermittent; BCVA; best-corrected visual acuity; CAS: Clinical Activity Score; VISA: Vision/Inflammation/Strabismus/Appearance

Table 3. Comparison of clinical parameters after treatment

Clinical parameter (mean, SD)	Before treatment	After treatment	*P*-values
Proptosis (mm)	20.2 ± 1.7	17.9 ± 2.3	0.028
logMAR BCVA	0.4 ± 0.2	0.3 ± 0.1	0.189
CAS	4.2 ± 0.4	1.4 ± 1.1	0.009
VISA	10.0 ± 1.4	4.2 ± 1.8	0.006

BCVA; best-corrected visual acuity; CAS: Clinical Activity Score; VISA: Vision/Inflammation/Strabismus/Appearance

The clinical outcomes of concurrent IVMP and OR are described in Table 2. Following treatment, there was a significant reduction in the mean CAS by 2.8 ± 1.3 (p = 0.009) and ITEDS-VISA scores by 5.8 ± 2.5 (p = 0.006) (Table 3). Improvement in proptosis measured by an exophthalmometer was noted, with a mean of 2.3 ± 1.5 mm (p = 0.028) (Table 3). Patient 3 exhibited an inadequate clinical response after OR and the second cycle of IVMP (similar visual acuity and optic nerve function test), necessitating endoscopic left orbital wall decompression surgery. After the fourth cycle of IVMP, the dysthyroid optic neuropathy resolved and remained quiescent throughout subsequent follow-up examinations. For Patient 4's condition improved after high-dose pulsed IVMP and OR and remained quiescent after the third cycle of IVMP. There was no need for an additional cycle after completing the course of treatment. The mean follow-up duration was 6.6 ± 5.4 months, during which no significant complications were noted.

Discussion

This was the first study in Malaysia demonstrating the outcome of concurrent high-dose pulsed IVMP and OR in the management of moderate-to-severe active TED. All patients were followed for at least 3 months after the intervention, which was the suggested optimal time to assess response to treatment.[10] All patients in the study achieved a reduction in CAS and ITEDS-VISA. Four out of 5 patients also achieved a reduction of ≥ 2 mm proptosis. The above improvement demonstrated a positive response to treatment, which corresponded with a recently revised composite index.[10] The composite index is composed of:

1. ≥ 2 mm reduction of lid aperture
2. ≥ 1 point reduction in 5-item CAS (no spontaneous or gaze-evoked pain)
3. ≥ 2 mm reduction in proptosis
4. ≥ 8° increase of eye motility.

An improvement in ≥ 2 features in 1 eye without deterioration in the fellow eye was considered a positive response to treatment.[10]

The 2021 European Group on Graves' Orbitopathy (EUGOGO) has recommended IVMP with a cumulative dose of 7.5 g per cycle as the first-line therapy and combination therapy of systemic corticosteroids and OR as the second-line treatment for active moderate-to-severe TED.[11] A previous review showed that the combination therapy of systemic corticosteroid and OR (70.2% of 392 patients) demonstrated a better response than patients who received only systemic corticosteroid (64.0% of 442 patients).[12] This was also proven by randomised controlled trials, which showed that OR synergistically potentiated the effects of systemic glucocorticoids.[13,14]

In our study cohort, we utilised a regimen involving high-dose pulsed IVMP every 3 weeks that deviates from the usual EUGOGO recommendations, which suggested a maximum cumulative dose of 8 g per course.[11] This approach was justified by

emerging evidence suggesting that such higher-dose pulsed schedules can improve outcomes. He *et al.* randomised patients to a monthly high-dose protocol (1.5 g IVMP per month for 3 months) versus a weekly protocol (0.5 g weekly for 6 weeks followed by 0.25 g weekly for 6 weeks) and found that, although overall response rates were similar, the monthly IVMP group achieved greater symptom improvement and lower recurrence rates than the weekly group.[15] Similarly, Young *et al.* evaluated early active TED patients treated either with pulses of 1 g IVMP for 3 days (18 g cumulative), every month, for 6 months or with the standard EUGOGO protocol, and found that the high-dose monthly regimen yielded excellent results and required fewer additional therapies.[16] Only 33% of pulsed IVMP patients needed adjunctive treatment versus 58% in the weekly dose arm, and no severe adverse effects were observed in the high-dose group.[16] In Japan, Tsujino *et al.* also employed a high-dose pulsed IVMP regimen of 1 g IVMP daily for 3 days, weekly for up to 3 weeks, and did not report any severe side effects including hepatotoxicity and cardiovascular events.[17] The concept of "cumulative toxicity" in IVMP was highlighted by Young *et al.* as something that should be reconsidered, as the mean residence time and systemic clearance of IVMP were 3.50 ± 1.01 h and 0.45 ± 0.12 1 h^{-1} kg^{-1}, respectively.[16,18] IVMP has a serum half-life of 1.93 ± 0.35 h, and is widely distributed to the tissues.[18] Taken together, these findings indicated that regimens with larger, spaced pulses provided more rapid and sustained relief of ophthalmic inflammation than conventional weekly IVMP, while also demonstrating a good safety profile.

Treatment with pulsed intravenous corticosteroids was more effective and better tolerated than with oral corticosteroids.[12] Regardless of the use of concurrent OR, the use of intravenous corticosteroids showed a greater improvement in diplopia, ocular motility, and proptosis compared to its oral counterpart.[12] The rate of side effects was lower with intravenous corticosteroids (56.1% vs 85%).[5] A few of the documented side effects of intravenous corticosteroids included urinary tract infections, glucose intolerance, and an increase in serum aminotransferase levels, which recovered spontaneously.[5] Patients in our study did not show any side effects from the use of IVMP.

On the other hand, OR was generally well tolerated, with minor side effects such as transient hair loss, lethargy, myalgia, headaches, insomnia, and nausea.[12] Our patients did not report any short-term side effects from OR, in agreement with previous studies.[19,20] However, the short follow-up period represented a limitation of our study, as it precluded detection of late complications, especially in the younger population. A retrospective study from Stanford investigated the long-term side effects of OR and found 5% of patients receiving OR had malignancies and 12% developed cataracts at a median time of 11 years.[21] Due to the concern of remote carcinogenesis, OR should be avoided in patients younger than 35 years.[11] While such long-term complications were not observed in our study cohort, further investigation with longer follow-up periods is warranted to assess the long-term safety of combination therapy in TED management.

In terms of long-term effectiveness, OR was effective in managing active TED, particularly ocular motility.[6] A review by Dolman and Rath recommended that concurrent OR and glucocorticoids should only be offered in the early active phase.[22] The initiation of OR within 6 months of proptosis resulted in a better reduction of proptosis, as the retro-orbital tissues are still in the acute or subacute inflammatory stage.[23] Patients who received OR with corticosteroids were also reported to have a lower risk of compressive optic neuropathy after an average follow-up of 3.2 years.[24]

Although thyroid dysfunction has been considered as a risk factor of TED,[1] recent evidence indicates that the development and progression of TED are independent of the thyroid dysfunction, and there is currently no evidence that managing hyperthyroidism with antithyroid drugs alters the natural course of TED.[25] In our cohort, patients who presented with hyperthyroidism were managed with antithyroid drugs under endocrinology supervision. Treatment for sight-threatening TED was prioritized in accordance with international consensus recommendations, with hyperthyroidism managed concurrently.[11,25]

The main limitation of this study was the small number of cases inherent to a case series design. Within this cohort, 2 patients had dysthyroid optic neuropathy, including 1 who underwent surgical orbital decompression. As dysthyroid optic neuropathy is the most severe form of TED with distinct management and prognosis, their inclusion may have influenced the overall outcomes. Given the limited sample size, separate subgroup analysis was not feasible; nonetheless, their clinical courses were reported descriptively.

In conclusion, our study provided evidence supporting the efficacy and safety of concurrent high-dose pulsed IVMP and OR in the management of moderate-to-severe active TED, especially in the degree of proptosis and inflammation. This combination therapy proved to be effective in the local population. However, this was a small case series analysis; hence further larger-scale research is warranted to validate these findings and optimise treatment protocols for managing TED.

Declarations

Ethics approval and consent to participate:
This study was conducted in accordance with the Declaration of Helsinki and, consent and prior ethical approval was obtained from the Medical Research and Ethics Committee of the Malaysian Ministry of Health (NMRR ID NMRR-24-01311-LMX).

Competing interests
None to declare.

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