Comparison of intravenous methylprednisolone therapy vs. oral methylprednisolone therapy in patients with Graves’ ophthalmopathy

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Introduction

Graves’ ophthalmopathy (GO), an autoimmune disorder of the retrobulbar tissue, is closely linked to autoimmune thyroid disease. It is a disfiguring and invalidating disease that profoundly impairs the quality of life of affected individuals (1). Less than 5–10% of patients with Graves’ disease will develop clinically relevant, active and progressive orbital complications to require medical or surgical intervention (2). Treatment of this disease is difficult and often unsatisfactory (3). Glucocorticoids have been used for treatment of GO because of their anti-inflammatory and immunosuppressive actions during the active phase of GO. Many studies have documented a high effectiveness of high-dose oral glucocorticoids (OGC) on soft tissue changes and optic neuropathy, whereas the decrease in proptosis and the improvement of ocular motility have not always been impressive (4,5). It has been reported that patients treated with high-dose intravenous glucocorticoid pulse therapy (IVGC) had a better outcome than those treated with OGC. However, IVGC was given in the interpulse periods, and followed by OGC treatment and/or orbital radiotherapy. These were not randomised and prospective studies (6–11). There was no study comparing directly the two modalities of GC administration, except that of Kahaly et al. (12).

The aim of this study was to determine whether IVGC therapy was more effective and better tolerated than OGC therapy in the management of GO.

Materials and methods

A prospective, randomised and single blind clinical trial was designed to compare IVGC with OGC monotherapy in terms of effectiveness and tolerability in Graves’ ophthalmopathy (GO). Fifty-two consecutive patients with untreated, moderately severe and active GO were randomly treated with either IVGC or OGC for 12 weeks. IVGC therapy achieved a more rapid and significant improvement than OGC therapy according to clinical activity score (p < 0.01), proptosis (p < 0.038), lid width (p < 0.0001), extraocular muscle changes (p < 0.02), optic neuropathy (p < 0.001), intraocular pressure (p < 0.04), visual acuity (p < 0.03), quality of life (p < 0.0001) and treatment response (p < 0.001). Diplopia was significantly improved in two groups but there was no difference between them (p < 0.6). Heavy smokers indicated alteration of ophthalmic signs with increased thyroid stimulating hormone (TSH)-receptor antibody during the therapy. In conclusion, IVGC therapy was more effective and better tolerated than OGC therapy in the management of GO.
Medical Ethics Committee of the Medical Faculty of Gaziantep University.

We included the patients who had moderately severe and active GO with a duration of <6 months. All patients were enrolled in this study after achievement of stable euthyroidism by use of the thionamide therapy. None of the patients had been previously treated for GO, except for eye drops without corticosteroids. Activity of GO was defined with a clinical activity score (CAS) of ≥4 points because of the high predictive value of CAS for the outcome of GC therapy (4). Assessment of activity of GO was performed with CAS based on the classification system proposed by Mourits et al. (4). and severity of GO was defined according to the criteria of the European Group on Graves’ Orbitopathy (EUGOGO) (3).

Exclusion criteria were corneal involvement (exposure keratitis, corneal ulceration, clouding or necrosis), contraindication to glucocorticoid therapy and patients who had already been treated with glucocorticoids or any other treatment such as surgery or radiotherapy.

The diagnosis of Graves’ disease was based on history of the presence of conventional symptoms of thyrotoxicosis associated with a diffusely enlarged goitre, elevated levels of serum thyroid hormones, and increased thyroidal 131I uptake, elevated titres of antithyroid stimulating antibody, antithyroglobulin antibody and antithyroid peroxidase antibody.

The diagnosis of GO was based on the presence of the typical clinical features in combination with enlarged extraocular eye muscles on a coronal computerised tomography (CT) of the orbits.

A complete ophthalmic examination was performed by the same ophthalmologist who was blind to the treatment given to the patients both before and 3 months after start of the therapy. The examination included evaluation of CAS, proptosis (exophthalmometer), lid width fissure, eye muscle function, applanation tonometry, Goldman perimetry and funduscopy.

**Assessment of disease activity**

Disease activity was assessed using the classification system proposed by Mourits et al. (4). The classification system (activity score) ranged from 0 to 10 points based on the classical signs of inflammation. Patients were determined by assigning 1 point each for the presence of spontaneous pain behind the globe, pain on attempted upgaze, redness of the conjunctiva, redness of eyelid, chemosis, swelling of the caruncle, eyelid swelling, increase of proptosis of ≥2 mm during a period of 1–3 months, decrease of eye movements in any direction ≥5 mm during a period of 1–3 months, and decreased visual acuity (VA) of ≥1 line(s) on the Snellen chart during a period of 1–3 months. A score of 6 points represents the maximum activity score (4).

Proptosis was measured with an Hertel exophthalmometer (reading of ≥20 mm) and pinhole VA was tested with the Snellen cart (expressed as decimal). VA and intraocular pressure (IOP) are reported separately. Diplopia was assessed subjectively in four grades: 1 = no diplopia, 2 = intermittent, 3 = inconstant and 4 = constant diplopia. Thickness of extraocular muscles (maximum coronal section area of the most hypertrophic rectus muscle in each eye) of all the patients was measured with orbital CT.

**Assessment of the severity of GO**

Severity of GO was assessed according to the EUGOGO (3). Moderate disease was defined as marked soft tissue swelling, and/or proptosis ≥25 mm, and/or inconstant diplopia (3).

**Smoking**

We assessed smoking as none, less (1–19 cigarettes/day), and more (≥20 cigarettes/day). Thyroid stimulating hormone (TSH)-receptor antibody (TRab) was measured only in heavy smokers.

**Study design**

Patients were randomly assigned either IVGC therapy (IVGC group) or OGC therapy (OGC group). Treatment information was sealed in envelopes to ensure randomisation with a 1:1 ratio for treatment modalities in blocks of 10 size. IVGC group received 500 mg of methylprednisolone in 100 ml of physiological saline as a 30 min i.v. infusion per weeks for 6 weeks then tapering the dose by 250 mg per weeks for 6 weeks. Oral methylprednisolone was given in decreasing doses: 72 mg for the first 2 weeks, 64 mg/day for 2 weeks, 56 mg/day for 2 weeks; thereafter the dose was tapered off by 8 mg per week for 6 weeks. Treatment period of IVGC and OGC was 12 weeks. The total cumulative doses of IVGC and OGC group were 4.5 and 4 g respectively. Oral dosage was adjusted with these studies (12,13).

Blood glucose, renal parameters and liver enzymes were evaluated once a week during glucocorticoid therapy.

**Assessment of treatment outcome**

We determined the treatment outcome with an improvement in CAS, diplopia, lid width fissure and proptosis at 3 months after start of the treatment (14). A response to the treatment was defined
according to major and minor criteria suggested by Bartalena et al. (15). Patients showing an improvement at least in two major criteria (variations in proptosis and lid width of ≥2 mm; appearance, disappearance or changes in the degree of diplopia; changes in the CAS ≥2 points; and changes on one-tenth or more in VA) and one minor criteria (soft tissue changes, self-assessment evaluation) were considered responders to the therapy. On the contrary, showing no changes or improvement in one major criteria and/or in one or two minor criteria were classified as non-responders.

Quality of life assessment
It was performed on the day of the start of treatment and 3 months later using the English language translation of the Graves’ Ophthalmopathy Quality of Life Questionnaire survey provided by Terwee and colleagues from the Netherlands was modified to suit the Australian population. Of the 19 questions asked, nine questions related to visual function and eight questions were about the psychosocial consequences of changed appearances (16,17).

Statistical analysis
Analysis was performed with a statistical package (SPSS version 10.0; SPSS Inc., Chicago, IL, USA). All data were presented as mean ± SD. Range was given for metric values. Frequencies were given for dichotomous variables. Baseline and post-treatment (at 3 months after treatment) values of dependent samples were compared with Wilcoxon’s signed rank test (for metric variables) and the McNemar test (dichotomous variables). Bonferroni correction was made to calculate the final test statistic. Comparisons between two independent samples were analysed by using the Mann–Whitney U-test (metric variables) or Fisher’s exact t-test (dichotomous variables). Delta values were used for comparisons between treatment groups. The correlation between data were examined using Spearman’s rank correlation \( r_s \). \( p < 0.05 \) was considered to indicate significance.

Results
All 52 patients completed the study. Twenty-five patients were treated with IVGC therapy (IVGC group) and 27 received OGC therapy (OGC group). There was no significant difference in the baseline clinical and biochemical features of the patients in the two treatment groups (Table 1).

We observed a higher percentage of favourable effects in patients treated with IVGC therapy compared with the patients treated with OGC therapy in terms of effectiveness, tolerability, side effects and quality of life (Table 2).

| Table 1 Baseline characteristics of the patients with GO |
| --- |
| **Characteristics** | OGC group | IVGC group | p |
| Number | 27 | 25 |
| Age (years) | 41.3 ± 12 | 44.3 ± 11 | ns |
| Sex (n) | | | |
| Men | 13 | 11 | ns |
| Women | 14 | 14 | ns |
| Duration of GO (months) | 1–5 | 1–5 | ns |
| Smokers, n (%) | | | |
| None | 18 (67) | 15 (60) | ns |
| Mild (1–19 cigarettes/day) | 6 (22) | 6 (24) | ns |
| Heavy (≥20 cigarettes/day) | 3 (11) | 4 (16) | ns |
| CAS | 5 ± 0.7 | 5.2 ± 0.8 | ns |
| Mean ± SD | (4–6) | (4–6) |
| CAS | 13 (48) | 11 (44) | ns |
| Diplopia, n (%) | | | |
| Proptosis | 21.8 ± 2 | 22.2 ± 2 | ns |
| Mean ± SD | (17–26) | (17–26) |
| TSH (µU/ml) | 2 ± 1.2 | 1.9 ± 1.3 | ns |
| Range | (1.5 ± 0.3) | (2.7 ± 1.9) |
| Free-T4 (ng/dl) | 1.3 ± 0.2 | 1.5 ± 0.3 | ns |
| Free-T3 (pg/ml) | 3.2 ± 1.8 | 2.7 ± 1.9 | ns |

GO, Graves’ ophthalmopathy; OGC, oral methylprednisolone; IVGC, intravenous methylprednisolone pulse; CAS, clinical activity score; TSH, thyroid stimulating hormone; ns, nonsignificant.

Assessment of disease severity and activity
According to the predefined criteria, 18 of 25 patients (72%) in the IVGC group had a higher treatment response at 3 months when compared with 13 of 27 patients (49%) in the OGC group (p < 0.001).

Ocular findings based on the criteria described in the assessment of disease activity and severity were significantly improved in both groups at 3 months after the start of therapy. However, the improvement in CAS (p < 0.01), proptosis (p < 0.038), lid width fissure (p < 0.0001), VA (p < 0.029) and IOP (p < 0.035) in the IVGC group were significantly higher than that in the OGC group at 3 months.

The degree of amelioration of diplopia was statistically significant in the IVGC group (p < 0.007) and in the OGC group (p < 0.012). On the other hand, differences between the two groups did not reach statistical significance (p < 0.06).

Optic neuropathy was significantly improved in five of six patients with subclinical involvement in the IVGC group. In the OGC group two of five patients showed improvement. There was a significant difference between the two groups (p < 0.001).
We observed that improvement in the inflammatory findings according to CAS values was delayed in heavy smokers compared with non-smokers (Table 3). In addition, increased levels of TRab were positively correlated with CAS (Table 4).

### Side effects

IVGC therapy (56%) was better tolerated than OGC therapy (81%) (p < 0.01). Weight gain was the most frequent complaint in both groups particularly in women. Two patients of the OGC group and one patient of the IVGC group had cushingoid features. Gastrointestinal adverse events were similar for two groups because patients had previous gastrointestinal complaints and used H2 receptor blockers during the therapy. Twelve per cent of the IVGC group suffered from palpitations and hot flashes on the day of treatment (Table 5).

### Assessment of quality of life

In the OGC group, 20 of 27 patients (76%) expressed an improvement in the visual functioning.
and 21 of 27 patients (78%) had an improvement in psychosocial changes (p < 0.0001). By comparison, in the IVGC group, 85% (21 of 25 patients) had an improvement in visual functioning (p < 0.0001) and 81% (20 of 25 patients) had an improvement in psychosocial changes (p < 0.0001). IVGC therapy seems to be more effective in improving the quality of life of patients in comparison with OGC therapy (p < 0.0001).

**Discussion**

This prospective, randomised and single blind clinical trial confirms that IVGC therapy had more favourable effects than OGC therapy in terms of effectiveness, tolerability, quality of life, and was also associated with a lower rate of side effects in euthyroid patients with untreated, moderately severe and active GO. Similarities of the cumulative doses and periods of treatment modalities for both groups made the comparison of IVGC therapy with OGC therapy possible.

Previous studies reported that patients treated with IVGC therapy had a better outcome than those treated with an OGC therapy (6–11). However, treatment followed by OGC treatment and/or orbital radiotherapy. In this regard, there was not any prospective and randomised study comparing directly the two modalities of GC administration except a recently published study. It is a randomised, prospective, and single blind trial of i.v. vs. oral steroid monotherapy in 70 euthyroid patients with untreated, active and moderately severe GO. Cumulative doses and period of treatment were similar to those of our study (12).

According to the predefined criteria, patients in the IVGC group had a higher treatment response (72%) at 3 months when compared with in the OGC group (49%) (p < 0.001). Kahaly et al. (12) found a treatment response of 77% in the IVGC group and 51% in the OGC group (p < 0.001).

Previous studies showed a high effectiveness of IVGC therapy on inflammatory signs and optic nerve involvement. Methylprednisolone acetate (range 0.5–

### Table 4 Correlations of the improvement in CAS with TRab in heavy smokers

|                | Baseline | 3 months | p    | Baseline | 3 months | p    | rs  | p     |
|----------------|----------|----------|------|----------|----------|------|-----|-------|
| n              | 7        | 7        | 0.016| 7        | 7        | 0.01 | 0.79| 0.001 |
| Mean ± SD      | 5 ± 0.3  | 3.4 ± 0.4|      | 28.4 ± 7| 34.4 ± 9.4|     |     |       |
| Range          | 4–6      | 2–4      |      | 16–41    | 23–55    |     |     |       |

CAS, clinical activity score; TRab, TSH-receptor antibody.

### Table 5 Comparison of side effects of glucocorticoid therapy in both groups

| Side effects       | OGC group (n = 27) (%) | IVGC group (n = 25) (%) | p     |
|--------------------|------------------------|-------------------------|-------|
| Events             | 22 (81)                | 14 (56)                 | 0.0001|
| Sex, n (%)         |                        |                         |       |
| Men                | 13 (59)                | 8 (67)                  |       |
| Women              | 9 (41)                 | 6 (33)                  |       |
| Weight gain (≥3 kg)| 6 (29)                 | 2 (8)                   |       |
| Cushingoid features| 2 (7)                  | 1 (4)                   | 0.0001|
| Gastrointestinal   | 2 (7)                  | 2 (8)                   | 0.01  |
| Hypertension       | 2 (7)                  | 0                       | –     |
| Palpitation        | 0                      | 3 (12)                  |       |
| Myalgia            | 4 (15)                 | 0                       | –     |
| Hyperglycaemia     | 1 (4)                  | 3 (12)                  | 0.001 |
| Depression         | 1 (4)                  | 0                       | –     |
| Palpitation        | 0                      | 3 (12)                  | –     |
| Sleepiness         | 4 (15)                 | 2 (8)                   | 0.001 |

OGC, oral methylprednisolone; IVGC, intravenous methylprednisolone pulse.
IVGC vs. OGC in Graves’ ophthalmopathy

1 g/day) had been used at different intervals and cumulative doses (ranges 1–21 g) (2). Other studies indicated that IVGC therapy was effective in 73–78% of the cases (8,18).

Our results suggest that both treatment modalities were effective in the majority of the patients on ocular findings, but IVGC therapy had a significant improvement in CAS (p < 0.01), proptosis (p < 0.038), lid width (p < 0.0001), optic neuropathy (p < 0.001), extraocular muscle changes (p < 0.02), VA (p < 0.04) and ocular pressure (p < 0.03). As expected, IVGC therapy was most effective on soft tissue changes (CAS) and optic neuropathy; however, proptosis was less responsive. A greater improvement in diplopia in the IVGC group was found but it was not significantly different from the OGC group (Table 2). These results are in line with the data of another study (12).

Another randomised trial of OGC vs. IVGC associated with orbital radiotherapy in the management of GO reported that high-dose IVGC seems to be more effective and better tolerated than the oral route. They found a significant reduction in proptosis, lid width, diplopia and optic neuropathy in both groups, but the degree of amelioration was not significantly different between the two groups. However, the final CAS value was significantly decreased in the IVGC group compared with the OGC group (19).

Tagami et al. (8) reported that high-dose GC showed an improvement in diplopia in 78% of patients, decreased proptosis in 52% and improvement in VA in around 30%, seen immediately after pulse therapy and before the subsequent use of oral GC to consolidate the efficacy. Other studies have also shown that consolidating doses of OGC did not increase the effect of IVGC (7,20).

We observed that IVGC therapy was better tolerated than OGC therapy. Side effects occurred in 56% of the patients in the IVGC group and 81% of the patients in the OGC group. Weight gain was the most frequent complaint in both groups. But cushingoid features were seen particularly in the OGC group. Hyperglycaemia, hot flashes, palpitation and sleepiness was frequently seen on the day of the therapy in IVGC group. On the other hand, sleepiness and myalgia was frequently seen in OGC group. Kahalay et al. (12) observed that IVGC were fairly tolerated. Our results were similar to those of this study except that gastrointestinal adverse symptoms were seen in the OGC group.

Side effects of oral GC treatment have also been reported in other studies, including psychosocial, diabetes, hypertension, weight gain and cushingoid features (18,21–23).

We did not observe increases in serum liver enzymes and renal parameters as has been observed in other studies because cumulative doses of our study were lower than those in other studies (12,24). The majority of patients in both groups were satisfied with the effects of treatment but the IVGC group demonstrated remarkable and earlier improvement in visual and also psychosocial changes, except heavy smokers. We observed a positive correlation between the levels of TRab and inflammatory findings in patients smoking more than 20 cigarettes/day during the therapy (Table 4). Smoking affects the immunological reactions in the pathogenesis of eye disease. They alter the structure of TRab, making it more immunogenic by hampering restoration of tolerance to antigens. In addition, smoking decreases the effectiveness of glucocorticoids in a dose-dependent manner during treatment (25,26). For this reason, doctors should urged patients to give up smoking. Our results are in line with other studies (2,12,25).

In conclusion, this prospective and randomised study confirms the favourable effects of IVGC therapy vs. OGC therapy in patients with moderately severe and active GO. IVGC achieved a more rapid and effective immunosuppression. The severity and clinical activity of GO are important in determining the need for glucocorticoid therapy. Controlled large randomised trials should be required for judging the effect of treatment in GO. It is not clear yet to which dosage and period of time of glucocorticoids improve GO. In addition, we may titrate the dosage against the clinical response. The lowest effective dose should be given for as short a time as possible. This approach may minimise the potentially serious side effects of glucocorticoids.

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