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High-dose intravenous corticosteroid therapy for Graves' opnthalmopathy

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ABSTRACT. In order to compare orai and high-dose iv corticosteroid therapy for Graves' disease, 25 patients with Graves' opnthalmopathy were treated with two weekly ìv injections of 1g of methylprednisolone diluted in 250-500 mi of physiological solution for 6 weeks, and were compared to a group of 26 patients treated with orai prednisone at a dose of 60-80 mg/day progressìvely reduced every 2 weeks for a total duration of 4-6 months. The efficacy of treatment was evaluated using thè ophthalmopathy index score. Patients were followed at 3, 6, 12 months, and afterwards yearly. Ali patients showed a significant ìmprovement in signs and symptoms of orbitai inflammation and a slight Ìmprovement in proptosis and diplopia. Relevant side-effects were reported from patients receiving orai therapy, but no significant side-effects were observed in patients treated with high iv doses; a few ca&es presented with gastric pain (highly sensitive to aluminium oxide or ranitidine), while most of thè patients referred to cutaneous rashes and a metal taste that disappeared some hours after thè infusion. Improvements observed after treatment have been stable in both groups. In conclusion, in addition to a lower incìdence of side-effects compared to thè classìc orai therapy, thè high-dose iv steroid therapy provides efficient and stable Ìmprovement in Graves' ophthalmopathy. (J. Endocrinol. Invest. *24:*152-158, 2001) ®2001, Editrice Kurtis

INTRODUCTION

Ophthalmopathy is a frequent and severe complication of Graves' disease. The majority of patients develops Graves' ophthalmopathy (GO) at thè presentation of thè disease, but up to 20% of patients can also present GO more than 2 years before or after thè onset of thè hyperthyroidism. Eye invol-vement in Graves' disease is clinically evident in 20-40% of patients, but computed tomography (CT) scan and magnetic resonance show that eye and orbitai involvement is present in up to 100% of patients with Graves' disease (1, 2). The pathogenesis of GO has not been yet clarified. It has been hypothesized that thè presence of com-mon antigens shared between thè thyroid and thè orbitai content may activate an autoimmune re-sponse to thè retroorbital constituents producing inflammation, edema, and venous stasis ending in GO (3-6).

The presence of thyrotropin receptor (TSHr) mRNA in retroorbital tissues was recently identified (7-9) supporting thè hypothesis that thè common anti-gen can be thè TSHr itself.

The medicai treatment ìs based on locai protective agents and various immunosuppressive measures such as systemic administration of corticosteroids alone ortogetherwith orbitai trradiation (10), cyclosporine (11), plasmapheresis (12), and ivgammaglobulins (13). The treatment with corticosteroids has been demonstrated effective, although it Ìs associated with a variety of side-effects due to thè amount of steroids used and thè duration of thè therapy (14). Recent studies (15) indicate a higher percentage of favorable results in patients treated with intravenous corticosteroids (IVCS), compared to those treated with orai corticosteroids (OCS). These results must be interpreted with caution because IVCS were associated with orai glucocorticoids, or azathioprine. In addition, thè selection of patients with different degrees of disease activity and duration mìght have influenced thè results. This report shows thè results of a randomized prò-spective study performed in order to directly compare OCS and IVCS.

Key-words: Graves' disease, autoimrnune response/disease, corticosteroids, intravenous administration and dosage, adverse effects, thyroid gland/hyperthyroidism.

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PATIENTS AND METHODS

Pat/ents

Starting in 1992, patients with Graves' disease and eye manifestations of GO coming to our clinic were included in thè therapeutic trial. They were randomly inserted into two groups, one receiving OCS, and thè other IVCS.

The diagnosis of Graves' disease was based upon clinical manifestations and laboratory findings. The ophthaìmopathy was present from 4 to 24 months before patient enrollment in thè trial but was not previously treated. Ali patients were euthyroid at thè time of therapy with glucocorticoids. Patients were excluded from thè study if a current or recent virai infection was recorded orfound positive after an orai glucose tolerance test for diabetes and/or in thè presente of gastrointestinal bleeding tested by hemo-occult test. Patients were also excluded if they had other contraindications for steroid therapy or if informed consent was not obtained. For each group, thè number of patients and clinical inforrnation are shown in Table 1. The two groups were not different, despite a significant higher ophthaìmopathy index score in thè group of patients treated with IVCS.

Treatment, assessment *of efficacy and follow-up*

Patients receiving thè orai therapy were treated with prednisone with an initial dose of 60-80 mg/day, with graduai reduction and withdrawal over 4-6 months. Patients receiving thè IVCS treatment were treated in thè hospital on a daily basis with methylprednisolone (Solumedrol, Upjohn SpA, Milan, Italy), at a dose of 1000 mg diluted in 250-500 m of NaCl 0.9% solution over approximately 2-h treatment. Iv administration of thè drug was performed for two consecutive days each week for a total of 6 weeks (12 administrations). The protocol received thè approvai of thè Ethical Committee. Eye changes were evaluated according to thè protocol suggestions for thè major world thyroid associations (16), and thè activity score and proptosis were cal^ulated and analyzed with thè Student's t-test for paired data and ANOVA test. Ali statistics were performed with thè StatView® 5.0 statistical program. Outliers were identified by a two-tailed test with a significance level of <0.05 (17, 18). No more than one outlier per treatment group was removed.

After treatment, patients were required to fili out a subjective questionnaire concerning their eye symptoms with a rating from +1 to +3 for improvement, from -1 to -3 for thè worsening (1 =mtld, 2=moderate, 3 = high), and O for no changes. Patients were also specifically interviewed for side-effects observed during thè treatment.

Ali patients receiving IVCS treatment completed thè study, while 3 patients treated with OCS therapy had to withdraw from thè treatment due to severe signs or symptoms of hypercortisolism (hy-perglycemia, polymenorrhea and centrai obesity, respectively). Patients were evaluated 3, 6 and 12 months after thè treatment, and then once a year. At each control point, patients received a clinical evaluation, laboratory thyroid functìon tests, and an ophthaìmopathy activity score.

Table 1 - *Clinical Information in thè two groups of patients.*

	Orai corticosteroids	Intravenous corticosteroids
Number of patients	26	25
Age (mean±SD)	44.57±14.8	42.6±13.1 (NS)
Sex	21 F/5 M	1 9 F/6 M
Smokers	6	6
Ophthaìmopathy index score before treatment	2.65±0.89	4.43±1.91 (p<0.001)
Proptosis before treatment	23.0±2.12	21.65±3.26(NS)

RESULTS

The effects of treatment on thè ophthaìmopathy index score and on thè proptosis are reported in Figure 1 and in Table 2. Columns represent means± SD of thè scores before and after treatment. Mean of activity score pre-treatment was 2.65±0.89 and 4.43±1.91, while after thè treatment it was 2.0±1.17 and 2.67±1.67 in patients that received thè OCS and IVCS therapy, respectively. In both groups, thè reduction was highly significant, with a p value of 0.001 for thè OCS therapy and <0.0001 in thè IVCS therapy. The ophthaìmopathy index score was reduced by 24.7% in patients receiving OCS and by 39.9% in patients receiving IVCS, with a p value <0.05, calculated by thè ANOVA test. Table 2 shows thè results observed for each of thè parameters studied for thè ophthaìmopathy index score and compared using thè t-test for paired data. The comparison of thè various parameters used for thè score calculation indicates a significant improvement in chemosis, eyelid edema and erithema, conjunctival injection and swelling of thè carun-cle in patients receiving IVCS, and only of eyelid erythema, and conjunctival injection in patients treated with OCS.

The proptosis was reduced from 23.7±1.84 to 21.07±2.79 mm (p<0.0005) in thè OCS patients

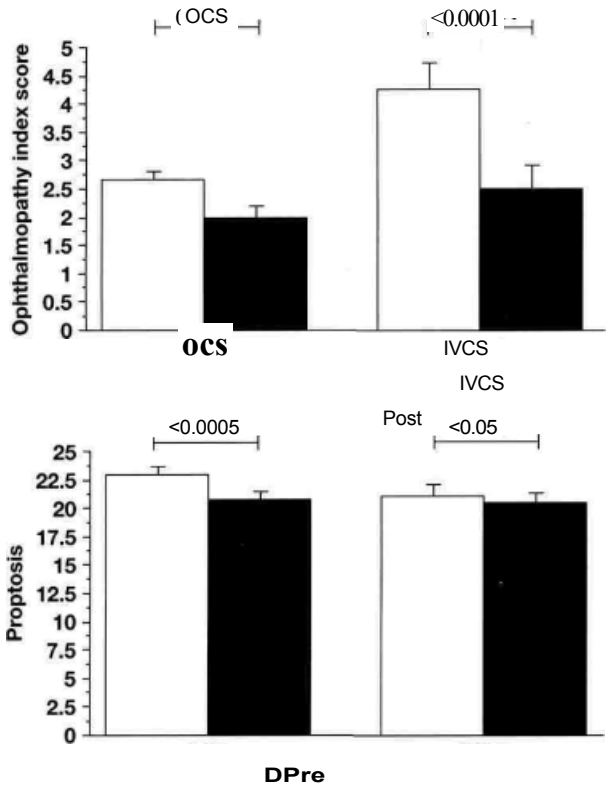

Fig. 1 - ***in*** **thè** ***figure are*** **reported mean va/ues±SE for ophtha/mopathy index score** ***(A)*** **and** ***for proptosis (B) before and after thè treatment in patients receiving orai corticosteroids (OCS) or ìntravenous corticosteroids (IVCS). The ophthal-mopathy index score*** **was ca/cu/ated according to thè sugges-t/ons** ***of thè*** **ma/or wor/d** ***thyroid association (16),*** **Both OCS and** ***IVCS treatments*** **determ/ned a** ***significant reduction of*** **thè ophtha/mopathy score but had no effect on thè** ***proptosis. The comparison of thè effects of thè two treatments with ANOVA*** **test** ***ìndicates no differences in thè efficacy of OCS and IVCS.***

and from 22.46±3.29 to 21.56±2.73 mm (p<0.05) in thè IVCS patients, with no differences in thè response calculated by 2-way ANOVA. The results of patient questionnaires recording thè subjective modifications after thè treatment are reported graphically in Figure 2. Subjective evaluation was performed one week after thè end of thè orai therapy or after thè last infusion of methylprednisolone. In thè case of IVCS treatment, it is worth noting that thè patients reported an improvement of thè eye conditions already starting from thè sec-ond/third week of treatment. Panel A displays thè data concerning each patient for both groups of treatment. Panel B summarizes thè results of thè questionnaire indicated as percentage of patients that noted an improvement in thè symptoms, percentage of patients in which thè personal symptoms remained thè same and percentage of patients who had a worsening of thè eye symptoms. In thè group of patients receiving IVCS treatment, 84% improved after thè treatment, 12% had no change, and 4% reported a worsening of symptoms. In thè group of patients treated with OCS, thè percentages were 57%, 35% and 8%, respectively.

Si de-effects

As already reported (14, 15), thè treatment with OCS produces relevant side-effects. In our study, thè more frequently observed side-effects were: in-creased blood pressure (26.9%), muscular pain (23.1%), appearance of centrai obesity (23.1%), fluid retention (15.4%), hyperglycemia (15.4%), pe-techiae and ecchymoses (11.5%), acne (11.5%), ir-ritability (8.0%) and polymenorrhea (3.8%). In 4/26 patients, thè treatment was withdrawn due to thè presence of severe side-effects.

Table 2 - ***Effects of treatment on thè parameters*** **stud/ed before and after thè treatment (p** ***values were*** **ca/cu/ated w/th a Student's t-test for pai'red data).**

	OCS-pre-treatment	OCS-after treatment	IVCS-pre-treatment	IVCS after treatment
Chemosis	0.33±0.22	0.23±0.22 {NS)	0.53±0.51	0.17±0.30{p<0.001)
Spontaneous pain	0.29±0.21	0.26±0.24 (NS)	0.50±0.51	0.43±0.50 (NS)
Pain on movements	0.34±0.22	0.30±0.26(NS)	0.60±0.50	0.50±0.51 (NS)
Eyelid edema	0.48±0.23	0.38±0.27 {NS)	0.77±0.43	0.50±0.57 (p<0.05)
Eyelid erithema	0.56±0.23	0.42±0.22 (p<0.05)	0.93±0.50	O.ÓO±0.51 (p<0.001)
Conjuntival injection	0.35±0.21	0.19±0.18(p<0.005)	0.53±0.51	0.03±0.18(p<0.0001)
Swelling of thè caruncle	0.30±0.20	0.22±0.21 (NS)	0.57±0.50	0.37±0.49 (p<0.05)
Tota l score	2.65±0.89	2.00±1.17 (p<0.001)	4.43+1.91	2.67±1.67(p<0.0001)
Proptosis	23.7±1.84	21.07±2.79(p<0.0005)	22.46±3.29	21.56±2.73(p<0.05)

IVCS: Ìntravenous corticosteroids; OCS: orai corticosteroids.

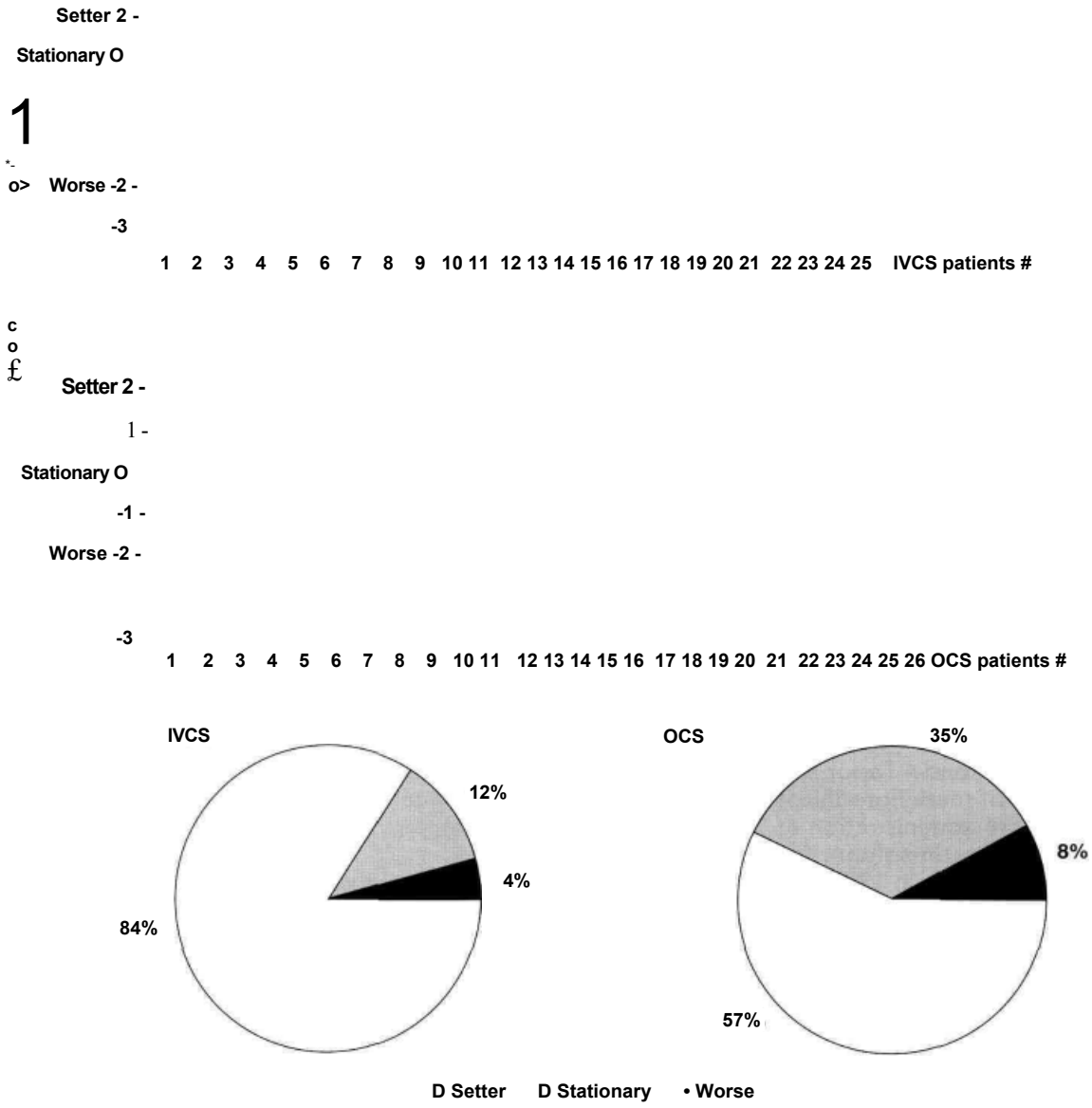

Fig. 2 - *A) Resuits* of thè subjectiVe score quest/onnaire. After treatment, patients were requ/red to rati'ng from +^ *to +3* for /m-provement, from -7 to -3 for thè worsening of thei'r eye symptoms. Zero *(0) indicates* stab/e situation. Each co/umn shows for each pati'ent thè entity of /mprovement or worsening of thè eye symptoms. *B) ìmprovements, worsening* and stab/e eye symptoms *expressed as percentage for* both groups of treatment *IVCS: intravenous* cort/costero/ds; OCS: ora/ corticostero/ds.

No relevant side-effects were observed during thè treatment with IVCS. The majority of thè patients (60%) reported gastric bum immediately after thè infusion or in thè following 24 h. The bum was highly sensitive to thè aluminum hydroxide treatment, and only 6 (24%) patients required ranitidine treatment. Cutaneous flushes appeared in 18/25 (72%) patients during thè first 2-3 h after thè infusion, but they disappeared spontaneously in ali patients. Some patients reported a "metal taste" during and immediately after thè infusion, which also disappeared spontaneously in a few hours. Only 2 patients had a slight increase of body weight, which returned to normal at thè first control of thè follow-up.

Follow-up

Ali thè patients of both groups are stili in follow-up. The results at thè end of treatment remained sta-ble and no relapse of thè ophthalmopathy, as mea-sured by thè ophthalmopathy index score, was observed during thè controis for more than 2 years after thè end of thè therapy.
Only one patient underwent orbitai decompression surgery for esthetic reasons.

DISCUSSION

The treatment of GO with corticosteroids was in-troduced more than 50 yr ago, though only recently have steroids been used in high doses by iv ad-ministration.
Nagayama et *al.* was one of thè first to test *in bolo* iv administration of corticosteroids for GO (19), demonstrating a regression not only in short-term, but also after severa! months. Unfortunately, his study reported results only on 5 patients, and 3 of them also received orai steroid therapy after thè iv treatment.
After Nagayama, Kendal Taylor et *al.* tested thè iv administration of methylprednisolone in 11 patients (20) by thè administration of 2 iv doses of 0.5 g of methylprednisolone, followed by thè long-term orai therapy. In 1991 and 1993, iv pulse therapy with methylprednisolone alone was pro-posed in meetings by Bromberg et *al.* (21); and Romaldini et *al.* (22) with excellent results not only on ocular manifestations, but also on thè oph-thalmic immunoglobulin levels. Hiromatsu *et al.* ìn 1993 used 3-5 times for 3-5 weeks 1 g of methylprednisolone in 15 patients, and 12 of them also received orai therapy for one month after thè last infusion. Diplopia and periorbital edema markedly improved after treatment in 9 patients, as well as proptosis values and intraocular pressure measurements which significantly de-creased (23).
In 1994 Koshiyama et *al.* tested iv steroids followed by orbitai irradiation in 8 patients with diplopia or fixed globes (24). After thè combined therapy, diplopia disappeared in 5 of them, one patient with fixed globes showed normal eye movement and two other patients exhibited great improve-ment, although their diplopia persisted. Extra-ocular muscle enlargement, assessed by magnet-ic resonance imaging, was also reduced after combined therapy.
More recently Ózmen et *al.* tested thè efficacy of IVCS therapy on a group of 9 patients demonstrating that good results can be obtained for thè im-provement of soft tissue inflammation, but not for proptosis (25).
In thè present study, we make thè first direct com-parìson of OCS and IVCS therapy for GO. Our results indicate that both treatments are efficient in thè stabie control of thè acute inflammatory signs of Graves' eye disease, producing a significant de-crease in thè ophthalmopathy index and a slight but significant decrease of thè proptosis. Intere-stingly enough, thè pain was not significantly reduced in patients treated with IVCS, even if thè patients reported a global improvement in their symp-toms starting from thè first weeks of treatment. The pitfall in this study is thè different length of thè two treatments, however thè selection of an ap-propriate control group for this comparison is al-most impossible, in fact thè orai treatment lasts for 4 to 6 months, while thè IVCS requires only 6 weeks. Patients receiving orai therapy reported a higher incidence of side-effects than patients treated with IVCS, in fact 3 out of thè 26 had to with-draw from thè treatment. Patients treated with IVCS reported only minor side-effects that resolved with-in a few hours after thè end of treatment. The typ-ical obesity and thè "cushingoid habitus" observed during long-term OCS therapy in 5 of our patients (out of 26) were not found in thè subjects treated with IVCS.
Finally, a major advantage of this treatment protocol ts thè full complìance of thè patients with thè IVCS, since they are required to be followed in thè hospital, and despite thè major cost of a single administration, thè total time to achieve effective results ts much shorter (6-7 weeks) compared to thè OCS administration (14-15 weeks). In conclusion, we propose high-dose iv methylprednisolone therapy as thè primary choice for treatment of GO, since it is as efficient as thè orai treatment and produces less side-effects, thus be-ing more easily accepted by patients.

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