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Clinical Results of Combined Systemic Steroid and Retroorbital Radiotherapy Treatment in Active Thyroid Associated Ophthalmopathy

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Abstract

Objective: The aim of this study is to evaluate the efficacy of a different steroid dosage protocol which consists of intravenous pulse methylprednisolone combined with retroorbital radiotherapy in the treatment of active thyroid associated ophthalmopathy.

Methods: The medical records of 29 patients who were treated with a standard protocol and who were followed-up for at least 6 months were retrospectively analyzed. The treatment protocol consisted of intravenous pulse methylprednisolone 1gram/day for 3 consecutive days, followed by retroorbital radiotherapy. Oral prednisolone which was tapered over a 3-month course was given as a maintenance dose.

Results: 58 eyes of 29 patients were included in the study. Twelve patients were female (41%) and 17 were male (59%) with a mean age of 47.7 ± 12.6 years. The clinical activity score was 4.8 ± 1.3 and 2.8 ± 1.2, before and after treatment, respectively ($P < 0.05$). 14 eyes (31%) had an improvement in best corrected visual acuity. In 28 eyes with had proptosis, proptosis regressed after treatment. Among 21 patients with diplopia, 13 (61%) patients reported an improvement in diplopia after treatment ($P < 0.05$). None of our patients had any adverse event due to systemic steroid and retroorbital radiotherapy.

Conclusions: Pulse intravenously applied methylprednisolone for 3 days as 1 gram/day, combined with retroorbital radiotherapy proved to be effective in control of moderate to severe and active thyroid associated ophthalmopathy. In the 6-month follow-up significant decrease in clinical activity score and improvement in diplopia was observed in addition to improvement in best corrected visual acuity.

Keywords: Orbital radiotherapy; Thyroid ophthalmopathy; Graves' disease

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Aktif Tiroid Orbitopatide Kombine Sistemik Steroid ve Retroorbital Radyoterapi Tedavisinin Klinik Sonuçları

Öz

Amaç: Bu çalışmanın amacı, aktif tiroid orbitopati tedavisinde retroorbital radyoterapi ile kombine intravenöz pulse metilprednizolondan oluşan farklı bir steroid dozaj protokolünün etkinliğini değerlendirmektir.

Yöntemler: Belirlenmiş standart protokol ile tedavi edilen ve en az 6 ay takip edilen 29 hastanın tıbbi kayıtları retrospektif olarak incelendi. Tedavi protokolü arka arkaya 3 gün 1 gram/gün dozunda intravenöz pulse metilprednizolon ve ardından retroorbital radyoterapiden oluşuyordu. İdame dozu olarak oral prednizolon 3 ay süreyle ayda bir doz azaltılarak verildi.

Bulgular: 29 hastanın 58 gözü çalışmaya dahil edildi. 12 hasta (%41) kadın, 17 hasta (%59) erkekti ve ortalama yaşları 47,7 ± 12,6 idi. Klinik aktivite skoru tedaviden önce ve sonra sırasıyla 4.8 ± 1.3 ve 2.8 ± 1.2 idi ($p < 0.05$). 14 gözde (%31) en iyi düzeltilmiş görme keskinliğinde iyileşme görüldü. Propitozisi bulunan 28 gözde tedavi sonrası propitozis geriledi. Diplopisi olan 21 hastadan 13'ü (%61) tedaviden sonra diplopide iyileşme bildirdi ($p < 0.05$). Hiçbir hastamızda sistemik steroid tedavisine ve retroorbital radyoterapiye bağlı yan etki görülmedi.

Sonuç: Pulse intravenöz 3 gün süreyle 1 gram/gün dozunda uygulanan metilprednizolon, retroorbital radyoterapi ile kombine edildiğinde aktif tiroid orbitopatinin kontrolünde etkili oldu. 6 aylık takipte en iyi düzeltilmiş görme keskinliğinde düzelmenin yanı sıra klinik aktivite skorunda anlamlı azalma ve çift görmede düzelme izlendi.

Anahtar kelimeler: Orbital radyoterapi; tiroid orbitopati; Graves' hastalığı

INTRODUCTION

Graves' disease is an autoimmune disorder that manifests itself with hyperthyroidism, diffuse goiter and ophthalmopathy. Ophthalmopathy is the most common extrathyroidal manifestation.

Although thyroid associated ophthalmopathy (TAO) is often seen in Graves' patients, it is an autoimmune disease of retroorbital tissue that can sometimes be seen in hypothyroid and even euthyroid patients[1,2].

Annual incidence of Graves' disease is 0.3% in the United States. Though Graves' disease is 6-7 times more common in women than in men, severe ophthalmopathy is more common in men. TAO usually begins between the ages of 30-50 and progresses more severely after the age of 50[3]. TAO commonly begins within 18 months after the initial diagnosis of Graves' disease. However, the onset of orbitopathy may be 10 years before or 20 years after the onset of thyroid disease[4]. About half of Graves' patients have ocular involvement but are generally mild; clinically significant disease occurs in 20-30% and there is a threat to vision in 3-5% of patients[5]. Clinical manifestations of TAO include exophthalmos, strabismus, periorbital edema, eyelid retraction, extraocular muscle dysfunction, conjunctival hyperemia, eyelid edema, chemosis and rarely compressive optic neuropathy. The most common complaints in TAO are pain, blurry vision, diplopia, epiphora and photophobia. Non-preventable risk factors for TAO are age, gender, genetic susceptibility. Preventable risk factors are smoking, stress, thyroid dysfunction, and radioactive iodine treatment.

TAO is known to be an autoimmune disorder. Autoimmunity occurs against common antigens in the thyroid gland and orbital tissue. It's known that autoantibodies occur against the thyroid stimulating hormone (TSH) receptor. In addition, autoantibodies have been reported to occur against calsequestrin[6] and orbital fibroblast membrane antigen collagen XIII[7]. Autoantibodies produced against Insulin-like growth factor-1 (IGF-1) have also been shown to increase orbital involvement[8]. Reactive T lymphocytes, which recognize the common antigen in the thyroid gland and orbit, infiltrate

the orbital and the extraocular muscles perimysium. Adhesion molecules stimulated by cytokines also contribute to this event. After infiltration of orbital tissue by T lymphocytes, the antigen is recognized by the T cell receptor on lymphocytes (Th). CD8+ lymphocytes are activated by cytokines secreted by Th lymphocytes. The cytokines cause the synthesis and secretion of the glycosaminoglycans (GAGs) by fibroblasts. Because of their water attracting properties, GAGs lead to proptosis, periorbital edema, and extraocular muscle swelling. Orbital fibroblasts contain preadipocyte cells which turn into adipocytes under hormonal stimulation. These cells also contribute to increased volume of retroorbital adipose tissue[9]. Peroxisome proliferator-activated receptor gamma activation of (PPAR-γ) is also important. This increases the adipose tissue in the retrobulbar region[10].

Lymphocytes which infiltrate the orbit are highly radiosensitive. Retroorbital radiotherapy (RT) is useful in the treatment of TAO, because it reduces glycosaminoglycan, hyaluronan deposition and has anti-inflammatory effect by promoting lymphocyte apoptosis[11,12]. RT should be combined with steroid therapy, since the effect of radiotherapy can take several weeks to begin, and radiotherapy initially causes temporary inflammation. The main effect of radiotherapy is on the extraocular muscles. Radiotherapy increases the motility of the globe and has a healing effect on diplopia. The contraindications of RT include inactive stages of TAO, patients younger than 35 years of age due to a theoretical risk and poorly controlled diabetes. The most serious side effect is the development of secondary malignancy, namely meningioma or pigmented basal cell carcinoma[13,14]. However long-term follow-up has not revealed a high incidence of radiation induced secondary tumors[15]. Ocular adverse effects include microvascular retinopathy, cataract, and conjunctivitis.

According to the EUGOGO criteria, intravenous methylprednisolone (ivMP) combined with oral mycophenolate sodium is the first line treatment for moderate to severe and active Graves' orbitopathy[16]. Corticosteroids provide clinical improvement in the acute phase of the disease, but not in the chronic period. Corticosteroids have immunosuppressive and anti-inflammatory effects and reduces GAG synthesis and secretion from fibroblasts. The effect starts quickly, symptoms will recover quickly. While orbital pain, injection, conjunctival edema, soft tissue inflammation and compression-induced optic neuropathy will recover rapidly, proptosis and improvement in ophthalmoplegia is less subtle. According to the EUGOGO guidelines, treatment consists of weekly intravenous injection of 500 mg of methylprednisolone for 6 weeks, followed by a weekly dose of 250 mg for 6 weeks. Intravenous (iv) route is more effective than oral route[17]. In a recent study which included 166 patients, high-dose ivMP (the cumulative dose of 7.5 g ivMP) treatment was applied and it was revealed that the most common side effect was asymptomatic changes in the laboratory values, and only 5% of patients developed severe side effects that would require discontinuation of the treatment[18]. Previous studies reported better outcomes in reducing the severity of TAO with combination of RT and iv glucocorticoids compared to iv glucocorticoids alone[19-21]. EUGOGO 2021 guideline proposed orbital radiotherapy combined with iv glucocorticoids as a second line treatment in the management of moderate to severe and active TAO, especially in patients with ocular motility disorders[16]. Still, there is no defined treatment dosage of the iv glucocorticoids. In this study, we aimed to evaluate the efficacy of pulse ivMP (1 gram daily for 3 consecutive days) followed by retroorbital radiation.

METHODS

The medical records of 29 patients who were treated with combined ivMP and retroorbital radiotherapy for thyroid orbitopathy in the ophthalmology and radiation oncology clinics of Cerrahpasa Medical Faculty between January 2012 and January 2019 were retrospectively analyzed. Patients who had CAS ≥ 3 and aged between 35 and 80 were included. Only patients who were followed-up at least 6 months after the treatment were enrolled in the study. Patients who had pregnancy, contraindication for receiving systemic corticosteroids or had medical history of diseases such as glaucoma and diabetic retinopathy were excluded. The study was conducted according to the tenets of the Declaration of Helsinki and ethical approval was obtained from the institutional review board (Cerrahpaşa Clinical Ethics Committee, Date: 02.06.2021, Approval Number: 103785).

Baseline and follow-up data collected included the best corrected visual acuity (BCVA) with Snellen chart, clinical activity score (CAS)[22] extraocular muscle functions, and presence of diplopia or proptosis. Proptosis (in millimeters) was measured with the Hertel exophthalmometer by the same practitioner. An exophthalmometry reading over 21 mm was considered pathological. The follow-up data was obtained from clinical reports 6 months after treatment. History of any ocular surgery (orbital decompression, extraocular muscle surgery) was noted.

Primary outcome was defined as treatment efficacy at 6 months follow-up. Treatment efficacy was determined according to improvement in CAS.

Treatment administration

Steroid treatment was applied for 3 consecutive days at a rate of 1 gram daily. Radiotherapy was delivered to the retroorbital field in 10 fractions with the total dose of 20 Gray by using a linear accelerator with 6 MV photon energy. Then, oral prednisolone with a dose of 48 mg for the initial month was given, the prednisolone dose was tapered monthly by half dose over a 3-month period (48 mg, 24 mg and 12 mg daily for the first, second and third month, respectively) Before receiving systemic corticosteroid, all patients were evaluated with an extensive work-up (electrocardiogram, chest radiography, glycated hemoglobin (HbA1c), full blood count, liver and kidney function test, hepatitis screen, tuberculosis and syphilis screening) to ensure they had no contraindications before ivMP treatment.

Statistical analysis

Descriptive statistics were expressed as mean and standard deviation (SD). Distribution of normal data was evaluated with Shapiro Wilk test. Statistical evaluation was made by Wilcoxon dependent value analyses and paired sample t test. p values below 0.05 was accepted as statistically significant. SPSS (version: 21.0) was used for the statistical analyses.

RESULTS

58 eyes of 29 patients were included in the study. 12 of the patients were female (41%) and 17 were male (59%). The average age of the patients at the time of initial admission was 47.7 ± 12.6 years. The CAS before and after treatment was 4.8 ± 1.3 and 2.8 ± 1.2 respectively, which demonstrated a statistically significance ($P < 0.05$). 9 patients (14 eyes) had an improvement in BCVA (31%). In 28 eyes with proptosis, the mean ophthalmometry measurement was 25.6 ± 2.4 mm before treatment and 23.1 ± 2.6 mm after treatment ($p > 0.05$). Among 21 patients who had diplopia before treatment, 13 (61%) reported an improvement ($p < 0.05$) (Table I). None of the patients reported worsening in diplopia. Orbital decompression surgery was performed in 3 (10.3%) treatment-resistant patients during the follow-up period. Among 29 patients, 26 (89.6%) showed treatment response and no

recurrence was observed during the 6-month follow-up period in treatment responsive patients. Radiotherapy-induced retinopathy and cataracts were not observed in any patients. None of our patients had any adverse event due to systemic steroid treatment.

DISCUSSION

The aim of this study was to demonstrate the efficacy of retroorbital radiotherapy combined with high dose pulse iv methylprednisolone therapy in moderate to severe and active TAO and observe the effect of this different dosage modality of steroid application in Graves' ophthalmopathy.

Our study is different from other studies in the literature in terms of the steroid regimen applied. Patients were given ivMP treatment for 3 consecutive days at a rate of 1 gram daily, then RT was applied and 3-month oral steroid treatment was given as a maintenance treatment. Oral steroid was given 48mg/daily for the first month and then 24 mg/daily for the second month and 12 mg/daily for the third month. In the 6-month follow-up after treatment it was observed that; CAS decreased, diplopia improved significantly, and BCVA increased in 31% of patients with clinical regression in proptosis.

None of our patients had any adverse event due to systemic steroid and RT. It can be said that the steroid applied at this level is a safe dose. Initial high dose with a short tapering time interval proved to be effective in 89.6% of patients in control of TAO with this new treatment regimen. Only 3 patients had treatment-resistant clinical findings and all 3 had undergone orbital decompression surgery. None of treatment responsive patients showed any recurrence during the 6-month follow-up period.

Different studies proved that combination therapy composed of ivMP and orbital radiotherapy was superior to iv steroid treatment alone in the management of moderate to severe and active TAO[19-23]. Recurrence rate was shown to be lower with combination therapy[21]. Besides, it was suggested that combined treatment with radiotherapy might compensate for lower steroid doses[20] which is in consistence with our findings.

Varying steroid dosage regimens were applied in the treatment of active TAO[20,21,23]. EUGOGO guideline recommends a cumulative iv steroid dosage of 4.5 gr over a course of 12 weeks when treatment is combined with mycophenolate sodium. When applied with RR there is no precise dosing for the iv. methylprednisolone. A study comparing the effectiveness of combined retroorbital irradiation plus iv steroids and iv steroids alone in the treatment of moderate to severe Graves' ophthalmopathy proved that the combination therapy was more effective[20]. In addition, simultaneous administration of ivMP and RT showed a more favorable effect compared to subsequent use of RT after ivMP, implying that RT should be carried out early concomitantly with ivMP[24]. In another study which included an ivMP cumulative dose at a range of 6-8 g showed that exophthalmometry readings, diplopia, CAS, and visual acuity improved significantly after treatment especially in females compared to males at 72-month follow-up[25]. In contrast, a study comparing the effect of pulse steroid therapy with or without retroorbital therapy revealed that there was no difference in proptosis and rectus muscle hypertrophy at the 6-month follow-up[26].

IvMP followed by oral prednisolone may not be solely effective to prevent recurrences in TAO. Previous studies reported recurrence rates between 9.5-20% within 6-12 months follow-up with ivMP alone whereas in our study, we observed no recurrences with combined treatment during the 6 months follow-up period[27,28]. Compressive optic neuropathy has

been shown to be less common in patients treated with combined corticosteroids and radiotherapy than in patients treated only steroids. Combined therapy has been shown to be protective against both optic neuropathy and disease progression[29].

Our study carries the limitations of retrospective studies, and the application of different steroid regimens cannot be compared. Performing a prospective study on the follow-up of TAO would be quite difficult due to the different clinical characteristics of each patient. Our study only includes clinical findings before and after treatment and no comparison in orbital magnetic resonance imaging or other laboratory findings were evaluated before and after treatment.

In conclusion, ivMP 1gr/day for 3 consecutive days and combined with radiotherapy in Graves's ophthalmopathy patients who have CAS ≥ 3 is an effective and safe treatment regimen. In our study, a higher initial dose of iv methylprednisolone with a shorter course of maintenance therapy was applied which proved to be safe and effective. Maintenance of oral therapy with tapering in 3 months is advised.

Ethics Committee Approval: The study was conducted according to the tenets of the Declaration of Helsinki and ethical approval was obtained from the institutional review board (Cerrahpaşa Clinical Ethics Committee, Date: 02.06.2021, Approval Number: 103785).

Conflict of Interest: The authors declared no conflicts of interest.

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