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Effect of Intravenous Methylprednisolone on the Signs & Symptoms of Graves' Ophthalmopathy

Muhammad Shah Alam[1], A. B. M. Kamrul-Hasan[2*], Syeda Tanzina Kalam[3], Ajit Kumar Paul[4], Shahjada Selim[5]

[1]Department of Medicine, Army Medical College, Cumilla, Bangladesh
[2]Department of Endocrinology, Mymensingh Medical College Hospital, Mymensingh, Bangladesh
[3]Department of Medicine, Cumilla Medical College Hospital, Cumilla, Bangladesh
[4]Department of Endocrinology, Mainamati Medical College, Cumilla, Bangladesh
[5]Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
Email: *rangassmc@gmail.com

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Abstract

Background: Graves' ophthalmopathy (GO) is the most frequent extrathyroidal manifestation of Graves' disease (GD). The effect of intravenous methylprednisolone on the signs and symptoms of GO has not been evaluated in the Bangladeshi population. **Objective:** To observe the effect of intravenous methylprednisolone in active Graves' ophthalmopathy. **Materials/Methods:** This prospective study conducted in a tertiary hospital of Bangladesh from May 2009 to November 2010 included 30 patients having moderate to severe ophthalmopathy. In addition to the clinical activity score (CAS), eye involvement was assessed by using the "NOSPECS" scoring system. **Results:** The mean (±SD) age of the patients was 38.1 ± 10.6 years and male-female ratio was 1.2:1. NOSPECS eye findings before treatment and during the final (3rd) visit of the patients were observed. It was found that lid retraction or lid lag was improved in 21 (70%) of the patients during the final visit. All of the patients had soft tissue swelling initially and all of them improved at the final visit. Bilateral proptosis was present in 19 patients before treatment and improved in 12 (62%) patients during the final visit. Right eye proptosis was present in 9 patients before treatment and improved in 5 (60%) patients during final visit. Extraocular muscle involvement (Diplopia) was present in 15 patients before treatment but improved in 13 (86.0%) patients during the final visit. A significant number of subjects showed significant improvement in all of the NOSPECS eye findings (except unilateral right eye proptosis) during the final visit; all had inactive GO (CAS < 2) at the end of the 3rd visit. **Con-**

clusion: Intravenous methylprednisolone appears to be an effective treatment option for active Graves' ophthalmopathy.

Keywords

Graves' Ophthalmopathy, NOSPECS, Methylprednisolone

1. Introduction

Graves' ophthalmopathy (GO) is the most frequent extrathyroidal manifestation of Graves' disease (GD) and develops in 25% to 50% of patients. Although the ophthalmopathy is mostly associated with Graves' hyperthyroidism, it may also less frequently occur in patients with hypothyroid or euthyroid subjects with GD. In its severe expression, it is a disfiguring and invalidating disease that profoundly influences and impairs the quality of life of affected individuals [1]. Patients with serious inflammatory Graves' ophthalmopathy should be treated with anti-inflammatory drugs and/or radiotherapy to prevent complications like fibrosis, while those with non-inflammatory ophthalmopathy may be treated by surgery immediately [2].

Treatment is based on the severity and activity of GO. The approach is suggested by the European Group of Graves' Orbitopathy (EUGOGO) consensus statement. Mild forms of GO may improve spontaneously and simply follow up and symptom management is usually sufficient. The therapeutic approach in patients with moderate-to-severe GO depends on whether the disease is "active" or "inactive". In patients with the active disease, an immunosuppressive or anti-inflammatory treatment, either systemic therapy and/or RT should be offered. In contrast, in patients with inactive GO, rehabilitative surgery should be considered. Finally, in patients with sight-threatening GO, first-line treatment is based on immunosuppressive or anti-inflammatory therapy but if there is a poor response or the disease is inactive, immediate surgical intervention is warranted. First-line treatment of active moderate to severe GO is systemic glucocorticoids, based on their anti-inflammatory and immunosuppressive effects. Intravenous glucocorticoids (ivGC) have a higher response rate and are better tolerated than oral [3].

Despite recent progress in the understanding of its pathogenesis and its management, major controversies still exist in different centers. Furthermore, we lack data on the effectiveness of different modalities of treatment options for GO. The current study was planned to evaluate to the efficacy of intravenous (iv) methylprednisolone (MP) on the signs and symptoms of GO.

2. Materials/Methods

2.1. Study Area

This prospective study was conducted in the departments of Endocrinology and

Ophthalmology of Bangabandhu Sheikh Mujib Medical University, Dhaka from May 2009 to November 2010 to observe the effect of intravenous methylprednisolone in Graves' ophthalmopathy.

2.2. Study Subjects

Thirty (30) diagnosed cases of active Graves' Ophthalmopathy of both sexes aging > 20 years who had not received any specific treatment for GO were enrolled for the study by purposive, convenience nonprobability sampling technique. The sample size was calculated with the assumption of the prevalence of Graves' disease 2% from previous studies (1% - 3%) and 5% margin of error [1]. Patients having acorneal ulcer, patients with static phage ophthalmopathy and those with any contraindication for iv MP therapy were excluded. Informed written consent was taken from all before the enrolment. In addition to their socio-demographic data, the eye involvement was assessed by using the scoring system "NOSPECS". The "NOSPECS" scheme is an acronym derived from the following eye changes: N = No signs or symptoms, O = Only signs (lid retraction or lag), no symptoms, S = Soft tissue involvement (periorbital edema), P = Proptosis (>22 mm), E = Extraocular muscle involvement (diplopia), C = Corneal involvement, S = Sight loss [3]. The extent and presence of proptosis were assessed by Hertel Exophthalmometer. Clinical activity of GO was assessed by Clinical activity score (CAS) of Graves' ophthalmopathy; patients with CAS > 2 were considered to have active GO [4]. All patients were treated with methylprednisolone 1 gm iv once daily for five consecutive days followed by atapering dose of oral prednisolone started with 60 mg per day. All patients kept in the hospital for at least one week, thereafter patients were under periodic follow up while putting on oral prednisolone for three months. A preformed semi-structured data collection sheet was used to collect data. The follow up was scheduled as the first visit- after giving five days of iv methylprednisolone, second visit after one month, and third visit after tapering dose of oral prednisolone. The changes (improvement or not) in NO SPECS parameters were noted in the follow-up visits as well as the development of any adverse events.

2.3. Statistical Analysis

Statistical analysis was done using Statistical Packages for Social Sciences (SPSS), version 19.0 software. All data were expressed as mean ± SD or median, or in percentages as appropriate. Chi-square test was used for comparison of the percentage of the subjects had an improvement in the NOSPECS parameters at the 3rd visit in comparison to the baseline. P-value ≤ 0.05 was considered to be statistically significant.

3. Results

The mean age of the study subjects was38.1 years and most of them were <40 years of age. 45% of them were female. Around half of them (45%) were hyper-

thyroid, 35% were euthyroid and the remaining 20% were hypothyroid. The eye involvement was bilateral in the majority (65%) (Table 1).

The percentage of study subjects showing improvement in the NOSPEC eye findings after the end of treatment is shown in Table 2. The majority of the subjects with NOSPECS signs and symptoms showed improvement. All 30 patients

Table 1. Baseline characteristics of the study subjects (N = 30).

Variables	Subgroup	Number of subjects (n)	Percentage (%)
Gender	Male	17	55
	Female	13	45
Age	38.1 ± 10.6 years (mean ± SD)		
Age Group	21 - 29 years	9	30
	30 - 39 years	10	35
	40 - 49 years	8	25
	>50 years	3	10
Thyroid Status	Hyperthyroid	14	45
	Hypothyroid	6	20
	Euthyroid	10	35
Eye involvement	Bilateral ophthalmopathy	19	65
	Unilateral ophthalmopathy	11	35

Table 2. NOSPECS eye findings before treatment and final visit (3rd visit) of the patients.

Components	No. of subjects having the specific component at enrolment	No. of subjects having changes in the specific component after methylprednisolone				*p
		Status	1st visit n	2nd visit n	3rd visit n (%)	
Lid retraction/lid lag	30	Improved	1	6	21 (70)	<0.001
		Not improved	29	23	9 (30)	
Soft tissue involvement	30	Improved	30	30	30 (100)	<0.001
		Not improved	0	0	0 (0)	
Bilateral proptosis	19	Improved	4	3	12 (63.2)	<0.001
		Not improved	15	12	7 (36.8)	
Right eye proptosis	9	Improved	2	2	5 (55.6)	<0.05
		Not improved	7	5	4 (44.4)	
Left eye proptosis	2	Improved	0	0	1 (50)	>0.05
		Not improved	2	2	1 (50)	
EOM involvement (Diplopia)	15	Improved	8	3	13 (86.7)	<0.001
		Not improved	7	4	2 (13.3)	
Clinical activity score	30	5 (median)			2 (median)	<0.001

EOM = Extraocular muscle.

had lid retraction/lag at the enrollment, 21 (70%) of them improved at the 3rd visit. Soft tissue involvement improved in all 30 patients. Bilateral proptosis improved in 63.2% (12 out of 19), unilateral left eye proptosis in 50% (1 out of 2), and unilateral right eye proptosis was improved in 55.6% (5 out of 9) subjects at the 3rd visit. Diplopia improved in 86.7% (13 out of 15) subjects at the final follow up. Moreover, at 3rd visit, all the study subjects were found to have inactive GO (*i.e.* CAS < 3).

4. Discussions

This prospective study was carried out to observe the effect of intravenous methylprednisolone in GO. A total of 30 patients ranging from 26 to 62 years with moderate to severe ophthalmopathy were included in the study.

In this study, all the study subjects had active GO (CAS ≥ 3) before receiving methylprednisolone; but after giving five days of one-gram intravenous methylprednisolone GO was inactive (CAS < 3) in all of them. Mourits *et al.* and van Geest *et al.* had similar observations [2] [5]. This implies that patients with an activity score of three or more beneficial effects from methylprednisolone may be expected.

At presentation, all of the 30 subjects had lid retraction and/or lid lag, all had soft tissue swelling, 19 had bilateral proptosis, 9 had unilateral proptosis of the right eye, 2 had unilateral proptosis of the left eye, and 15 had extra-ocular muscle involvement (diplopia). NOSPECS eye findings were reevaluated during 1st visit after giving five days of one-gram intravenous methylprednisolone and it was found that soft tissue involvements improved in all patients (100%). Bilateral proptosis improved in four (23.1%), right eye proptosis improved in two (20.0%) and none had improvement of left eye proptosis. Extraocular muscle involvement (Diplopia) was present in 15 patients which improved in eight (53%) patients. In a study Kendall-Taylor *et al.* showed that the response was often quite dramatic by 24 hours after the first dose of intravenous methylprednisolone, both when assessed subjectively and when evaluated objectively, this was most noticeable as a decrease in inflammation and proptosis with an improvement in visual acuity and therefore possibly represented a decrease in orbital edema rather than immunosuppression at that stage, which is similar to this study [6].

NOSPECS eye findings were also observed after three months of a tapering dose of oral prednisolone final visit (3rd visit). Improvements in lid retraction and/or lid lag were found in 21 (70%) out of 30 patients, bilateral proptosis in 12 (63%) out of 19 patients, right eye proptosis in 5 (56%) out of 9 patients, left eye proptosis improved in 1 (50%) out of 2 patients and extraocular muscle involvement (diplopia) improved in 13 (87%) out of 15 patients. Van Geest *et al.* have shown that the qualitative treatment outcome was successful at the end of the trial in five out of six (83%) patients receiving MP. They have shown that diplopia improved in 50% (two out of four) patients receiving intravenous methylprednisolone, in this study diplopia improved in 13 patients (86%), out of 15

patients [5]. Wiersinga *et al.* reported that supportive measures alone are inadequate, and oral prednisone in high doses of 40 to 140 mg daily improved visual acuity in 73.0% of 56 patients in one to two weeks. When intravenous pulses of methylprednisolone were administered followed by oral prednisone, 94.0% of 16 patients improved in one to seven days. The response rate to orbital irradiation (combined in one-third of patients with oral predisolone) was 79.0% in 44 patients [7]. All these results support the present study.

The efficacy of treatment was evaluated by using the ophthalmopathy index score done by Macchia *et al.* [8]. Patients were followed at 3rd, 6th, 12th months, and afterward yearly. All patients showed a significant improvement in signs and symptoms of orbital inflammation and a slight improvement in proptosis and diplopia. Relevant side-effects were reported from patients receiving oral therapy, but no significant side-effects were observed in patients treated with high intravenous doses. These findings are consistent with the current findings.

5. Conclusion

Intravenous methylprednisolone is an effective treatment for active Graves' ophthalmopathy. Most of the subjects with active GO showed improvement in the signs and symptoms of GO which were measured as NOSPECS in this study.

Limitations of the Study

Randomization was not done and the study lacks a control group having a placebo. Another drawback of the study is that longtime follow up was not done; so the possibility of relapse of GO after MP treatment could not be evaluated.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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