ORIGINAL ARTICLE

INVESTIGATING THE INTERPLAY: UNRAVELLING THE IL-6 CONNECTION AND INTRAVENOUS METHYLPREDNISOLONE'S IMPACT ON RECTUS MUSCLE IN THYROID EYE DISEASE

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ABSTRACT

Introduction & Objective: *Intravenous corticosteroid has been used in management of Thyroid Eye Diseases (TED). Many previous studies have shown the therapeutic benefits of corticosteroid therapy. Recently, the efficacy of high-dose intravenous corticosteroid pulse therapy has been reported. Recent studies have highlighted the potential role of interleukin-6 (IL-6) in the pathogenesis of TED. However, the correlation between IL-6 levels and the effects of IVMP on rectus muscles in patients with TED remains unclear. This study aims to investigate the correlation between IL-6 levels and the effects of IVMP on rectus muscles in patients with TED*

Methods : *Retrospective analysis were used in the data collection of patients with active Thyroid Eye Disease who undergone high-dose intravenous methylprednisolone pulse therapy (500mg per week for 6 successive weeks) at Sardjito General Hospital between January 2022 and December 2022. Data on the Level of IL-6 were obtained at the start of treatment, and quantitative computed tomography (CT) of the orbit and were performed before and after treatments. Demographics data were presented in tables and graphs.*

Results : *This study included 62 eyes of 31 patients (61,3% female) with mean age of 37.8±13.47 years old. There was significant inverse correlation in levels of IL-6 and ΔSR (P=0.037) which implies a reduced effect of IVMP on SR. However, other statistical analyses on different rectus muscle groups bare no statistical significance.*

Conclusion : *The use of IL-6 as a single predictor of responsiveness of the treatment of high dose intravenous methylprednisolone is not endorsed by the result of this study. However, further studies with better established level of IL-6 both pre and post treatment, and more inclusive parameters are needed to better provide better understanding on the role of IL-6.*

Keywords*: Thyroid Eye Disease, Intravenous Corticosteroid Therapy, Rectus Muscle, Extraocular Muscle, IL-6.*

INTRODUCTION

Graves' ophthalmopathy is a chronic autoimmune process that affects the retrobulbar tissue and has strong etiological links with autoimmune thyroid disease. Symptoms include blurring of vision, proptosis, extraocular muscle dysfunction, eyelid swelling, chemosis, redness of the conjunctiva, pain, lid lag, and retraction.

Interleukin-6 (IL-6) is a pleiotropic cytokine and plays a role in the regulation of immunological, neuroendocrinological and inflammatory processes. This cytokine is synthesized by different cells including monocytes, macrophages, fibro- blasts, endothelial cells

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and thyrocytes, as well as keratinocytes. Conditions causing thyroid cell damage are associated with the release of IL-6 cytokine, eventually with its high serum concentration.

During the active inflammatory stage, the retrobulbar tissue shows marked lymphocytic infiltration and interstitial oedema. Thus, immunosuppression is often used initially, and by suppressing inflammatory changes it can result in subjective and objective improvement of the disease. Many previous studies have shown the therapeutic benefits of steroid therapy. Recently the efficacy of high-dose intravenous steroid pulse therapy has been reported. Patients treated with high-dose intravenous steroid had a better outcome than those treated with an oral dose of steroid.

METHODS

This is a retrospective hospital based study conducted at Sardjito General Hospital in Yogyakarta from January 2022 and December 2022. All patients who were diagnosed with Thyroid Eye Disease based on the presence of conventional symptoms associated with history of hyperthyroid disease diagnosed by endocrinologists, who undergone high-dose intravenous methylprednisolone pulse therapy (500mg per week for 6 successive weeks) are included in the study.

The procedure processes were fully explained to each patient and written informed consent was obtained as documented on medical records. Laboratories data on Interleukin 6 (IL-6) were collected from medical records. The patients were divided into groups on the basis of age (<40 years old and ≥40 years old), gender (male and female). The extraocular muscle thickness data were measured using quantitative contrast head MSCT scan measured before and after injection. Scans were analysed by consultant radiologist in RSUP DR. Sardjito hospital and then uploaded in electronic medical records. Complications during and following procedure were noted in medical records. Continuous variables were expressed as the mean ± standard deviation for those displaying normal distribution. Pearson correlation test was used to demonstrate the correlation of IL-6 and baseline extraocular muscle, and IL-6 and delta extraocular muscles before and after IVMP. All of the statistical analysis was performed using SPSS software. P-values less than 0.05 were considered statistically significant.

RESULTS

This study included 62 eyes of 31 patients with mean age of 37.8±13.47 years old. The male to female ratio were 1:1.58 (61,3% female). Laboratories parameters that were analysed in this study were IL-6 (mean 1.83±0.86 pg/mL)

Table 1. Profile Cases of IV MP Pulse Therapy TED Patients

Age (years)	Frequency	Percentage (%)	Mean ± SD	Range
<40	16	51.6	37.8±13.47	20-61
≥ 40	15	48.4		
Gender			M:F ratio	
Male	12	38.7	1:1.58	
Female	19	61.3		
Affected eye			OD:OS ratio	
OD	31	50.0	1:1	
OS	31	50.0		
Lab Parameters	Frequency	Percentage	Mean ± SD	Range
IL-6	31	100.0	1.83±0.86	1.50-5.17

Table 2. Age and Gender Wise Distribution of Baseline Extraocular Muscle Thickness, UCVA and IOP

Age (YO)	Frequency	IR	MR	SR	LR
<40	32	4.30 ± 1.74	3.93± 1.05	3.76 ± 1.45	3.49± 1.04
≥ 40	30	4.61 ± 1.87	4.36± 1.97	4.50 ± 2.76	4.41± 1.96
p-value		0.505	0.283	0.190	**0.025**
Gender	Frequency	IR	MR	SR	LR
Male	24	5.16 ± 2.36	4.44±2.20	4.40 ± 2.98	4.05± 2.30
Female	38	4.00 ± 1.16	3.95±0.97	3.87 ± 1.50	3.86± 0.98
p-value		**0.013**	0.234	0.275	0.671

The findings in our study shows majority of the cases were in age group <40 (51.6%) and female (61.3%) in accordance with the previously known studies that TED commonly occurred in female, age before forty. [6] Previous study shows that the thickness of the extraocular muscles increases up to the middle age, then it starts decreasing, there was slight difference between the genders as males have thicker muscle than females.

There were significant differences between baseline data for the LR thickness in age group, and IR thickness in gender group.

Table 3. Comparative Analysis Baseline and IL-6

	Mean ± SD	IL-6 correlation	P-value
IRMT baseline	4.45±1.80	-0.033	p=0.797
MRMT baseline	4.14±1.57	0.117	p=0.365
SRMT baseline	4.12±2.20	0.196	p=0.128
LRMT baseline	3.93±1.61	0.019	p=0.883

Statistical analysis of the baseline extra ocular muscle thickness showed no statistical significance (P-value ≤0.05) in correlation with IL-6 despite showing greater increase in extraocular muscle thickness in almost all four muscle groups.

Ophthalmol Ina 2023;Supplement Ed.: 200-204

Table 4. Association and Correlation of IL-6 in IV MP Pulse Therapy Results

	Δ IR	Δ MR	Δ SR	Δ LR
IL-6	-0.031	-0.114	-0.266	-0.030
p-value	0.810	0.379	0.037	0.817

Statistical analysis on the delta extraocular muscle thickness with IL-6 revealed ΔSR to have lesser reduction correlating with level of IL-6 with statistical significance (P-value ≤0.05).

DISCUSSION

TED which leads to extraocular muscle oedema that restrict motility and cause diplopia is an intricate disease with cellular immunity process at the heart of it. Cellular immunity with activation of B-lymphocytes induces secretion of numerous cytokines - one of which is interleukin 6 (IL-6) - exert its action on orbital fibroblast, inducing its differentiation into a mature adipocyte. This leads to a hypertrophy of orbital fat, oedema of the orbital muscles and connective tissue, as well as signs of inflammation. [1,4]

In contrast to previous study, which stated a strong correlation of the enlargement of extraocular muscle with IL-6, the baseline of extraocular muscle thickness in this study shows no statistical significant correlation with the level of IL-6. This may be due to lack of data from TED severity group (EUGOGO or CAS Score), disease duration, and/or difference in sample population. [8]

Increased orbital fat and immune cells infiltration increase the volume of orbital soft tissue, leading to venous congestion and proptosis. Worsening congestion can compress the optic nerve, leading to neuropathy and permanent vision loss. Elevated orbital pressure can lead to forward protrusion of the eye, known as exophthalmos. [11]. IVMP is the well choice of the treatment due to its anti-inflammatory and immunosuppressive actions. [1,12]

Statistical analysis in this study were revealed to be insignificant may be due to several factors, one of which is the inability of a CT Scan imaging to provide sufficient data on orbital fat size in which the IL-6 play major role. However, this study suggest an inversive correlation between IL-6 and ΔSR with proper statistical significance, which implied a reduced effectiveness of IVMP therapy. [4.8]

As aforementioned, several factors serve as limitation within the scope of this study. Lack of data on disease characteristic of each patient (i.e. duration, severity), absence of other cytokines measurement which may play a significant role in disease development, and shortcoming in the measurement of IL-6 post IVMP therapy.

CONCLUSION

The use of IL-6 as a single predictor of responsiveness of the treatment of high dose intravenous methylprednisolone is not endorsed by the result of this study. However, further studies with better established level of IL-6 both pre and post treatment, and more inclusive parameters are needed to better provide better understanding on the role of IL-6.

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