

COMPARISON OF SERUM AND VITREOUS TGF-B1 LEVELS IN PROLIFERATIVE DIABETIC RETINOPATHY WITH AND WITHOUT PANRETINAL PHOTOCOAGULATION LASER THERAPY

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APPROVAL LETTER

No : 515/UN4.6.4.5.31/PP36/2021

Date : 27 March 2015

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IRB Protokol No	UH15010021	Sponsor Protocol No	
Principal Investigator	dr. Rosmiaty Z.A	Sponsor	
Title	Serum and Vitreous TGF 1 Levels With or Without Laser Panretinal Photocoagulation in Patients with Prolidratve Diabetic Retinopathy		
Protocol Version No	2	Version Date	25 March 2015
ICF Version No	2	Version Date	25 March 2015
Location	Hasanuddin University Hospital, Dr. Wahidin Sudirohusodo Hospital and Eye Centre orbita Clinic Makassar		
Type of review	<input type="checkbox"/> Exempted <input checked="" type="checkbox"/> Expedited <input type="checkbox"/> Full board	Duration of Approval From 27 March 2015 To 27 March 2016	Frequency of continuing review
IRB Chair	Name Prof.Dr .Suryani As'ad,MD, M.Sc,SpGK(K)	Signature 	
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- Submit progress report every 6 months for high-risk study, and yearly for low-risk study
- Submit final report after completion of protocol procedures at the study site
- Report protocol deviation / violation

Comparison of serum and vitreous TGF- β 1 levels in proliferative diabetic retinopathy with and without panretinal photocoagulation laser therapy



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ABSTRACT

Introduction: A long-term diabetic retinopathy will cause an increase in several growth factors expression like Transforming Growth Factor β (TGF- β). This multipotent cytokine is involved in the process of endothelial cell proliferation. Therefore, this study aims to observe the relationship between TGF- β 1 levels in serum and vitreous fluid of Proliferative Diabetic Retinopathy (PDR) patients given Pan Retinal Photocoagulation (PRP) laser therapy.

Method: This was a cross-sectional study involving 14 patients with PDR. TGF- β 1 levels of vitreous and peripheral blood were measured using Enzyme-linked Immunosorbent Assay (ELISA) method. The data were statistically analyzed using SPSS software for Windows ver. 23.0 for Mann-Whitney and the Spearman correlation test.

Results: Our subjects consisted of 57.1% males with a mean age of 51.8 years, where dyslipidemia was the most common comorbid disease. Mean serum TGF- β 1 level was $12,821.43 \pm 5,253.16$ pg/ml, while the mean value in vitreous was $3,692.86 \pm 333.89$ pg/ml. Meanwhile, there was no significant difference in serum and vitreous TGF- β 1 levels between subjects with and without PRP laser therapy ($p > 0.05$).

Conclusion: There was no significant correlation between TGF- β 1 levels in proliferative diabetic retinopathy patients with and without panretinal photocoagulation laser therapy. However, there was a decreasing trend in TGF- β 1 levels in the vitreous fluid, indicating that PRP laser therapy has a positive effect on preventing the formation of neovascularization in the eye.

Keywords: TGF- β 1 levels, proliferative diabetic retinopathy, panretinal photocoagulation laser.

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INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia due to the failure of the pancreas to produce sufficient insulin or the occurrence of cell resistance in peripheral tissues.¹ This condition can cause damage to various organs, including the heart, kidneys, and eyes, and even become a risk factor for death from complications.^{2,3} Epidemiological estimates in several studies predict that patients with DM will reach 380 million in 2025, with 4 million being at risk for visual loss due to Diabetic Retinopathy (DR).⁴

Diabetic retinopathy is classified into an early stage, namely Non-Proliferative Diabetic Retinopathy (NPDR), and an advanced stage, called Proliferative Diabetic Retinopathy (PDR).⁵ The case of a decrease in visual ability occurs due

to two mechanisms, namely increased intraretinal vascular permeability, which leads to macular edema and narrowing of the capillary blood vessels' lumen, to cause macular ischemia.⁶

The state of DR in the long term causes an increase in the expression of several growth factors such as Vascular Endothelial Growth Factor (VEGF), Platelet-Derived Growth Factor (PDGF), basic Fibroblast Growth Factor (bFGF), and Transforming Growth Factor beta (TGF- β).⁷ These biochemical molecules are known to trigger the occurrence of PDR, which leads to the threat of permanent blindness in patients.⁸ TGF- β is a multipotent cytokine that works through activin receptor-like kinase-1 (ALK1) and 5 (ALK-5).⁹ It is involved in endothelial cell proliferation, formation and degradation of extracellular matrix,

and chemotactic and apoptotic processes that lead to the thickening of the capillary basement membrane and impaired systemic blood vessels' regulation.⁸⁻¹⁰

The best treatment for RD patients is to control their blood sugar levels,¹¹ also, the therapeutic outcome is not aimed at curing or restoring visual function but at slowing the progression of vision loss.¹² Panretinal photocoagulation (PRP) laser therapy reportedly effectively fulfills these goals.¹³ It is performed when high-risk PDR is found to numb the ischemic area, thereby inhibiting further neovascularization.¹⁴

This study investigates the relationship between TGF- β 1 levels in serum and vitreous fluid of PDR patients given PRP laser therapy. The results are expected to form the basis for preventing further complications in DM patients, specifically those already having visual complaints.

MATERIAL AND METHODS

Study Design

This study was a cross-sectional study involving 14 patients with PDR who had vitrectomy surgery. The history and laboratory tests were conducted to confirm the diabetic status of patients by checking fasting blood sugar and HbA1c levels. Furthermore, routine ophthalmological examinations were carried out, including visual acuity test, intraocular pressure (IOP), examination of the anterior segment of the eye with slit-lamp biomicroscopy, and the posterior segment using funduscopy. The fundoscopic examination results were normal for NPDR and PDR, but only patients with PDR were analyzed. Furthermore, an analysis was conducted to assess the relationship between the duration and number of laser burns given to patients and the changes in TGF- β 1 levels examined in the serum and vitreous fluids.

Sample Collection

Vitreous samples were taken using a vitrectomy machine with a volume of 700-1000 μ l, while the serum using 3-5 ml blood samples was taken through the median cubital vein. Afterward, they were placed into a vacutainer tube for mobilization and storage.

TGF- β 1 Assay

TGF- β 1 levels were checked using the human TGF- β 1 ELISA reagent kit (Cat. No. MN 55412, R & D Systems, Inc, Minneapolis, USA), where the standard range on the device was 31.2 – 2,000 pg/ml with a detection limit of 4.61 pg/ml.

Processing and Data Analysis

The data were grouped according to the purpose and type of data. Then, they were statistically analyzed using SPSS software for Windows ver. 23.0. The normality test showed that the data distribution was

abnormal. Hence, the Mann-Whitney and the Spearman correlation test were used (Sig. $p \leq 0.05$).

RESULTS

Observations were made to determine serum and vitreous TGF- β 1 levels in patients with PDR with or without laser PRP. It was performed on 14 respondents with PDR who had experienced vitrectomy surgery. The univariate data presented in Table 1 shows that the study subjects consisted of 57.1% males and 42.9% females with a mean age of 51.8 years. The most common comorbid disease was dyslipidemia, with 50.0%. The mean serum TGF- β 1 level was $12,821.43 \pm 5,25$ pg/ml, while the mean TGF- β 1 level in vitreous was $3,692.86 \pm 333.89$ pg/ml.

Table 2 shows the comparison of

TGF- β 1 levels between patients treated with and without PRP laser therapy. The statistical calculations showed no significant association ($p > 0.05$) between serum and vitreous TGF- β 1 levels in patients with PDR with or without a history of PRP laser therapy. However, there was a decreasing trend in TGF- β 1 levels in the vitreous fluid, indicating that PRP laser therapy has a positive effect on preventing the formation of neovascularization in the eye.

DISCUSSION

The number of male patients in this study was more than females, while the mean age was 51.8 years and the most common comorbid disease was dyslipidemia. According to Jeffrey G et al. (2011), the development of DR in

Table 1. Descriptive data of samples.

Characteristics	N	(%)
Gender		
Male	8	57.1
Female	6	42.9
Age		
<50 years	3	21.4
≥ 50 years	11	78.6
Comorbidity		
Dyslipidemia	7	50.0
Hypertension	6	42.9
No comorbid	1	7.1
Serum TGF-β1 levels (mean \pm SD)		$12,821.43 \pm 5,25$
Serum TGF-β1 levels With PRP Laser Therapy		
≤ 12000 pg/ml	3	21.4
> 12000 pg/ml	5	35.7
Serum TGF-β1 levels Without PRP Laser Therapy		
≤ 12000 pg/ml	4	28.6
> 12000 pg/ml	2	14.3
Vitreous TGF-β1 levels (mean \pm SD)		$3,692.86 \pm 333.89$
Vitreous TGF-β1 levels With PRP Laser Therapy		
$\leq 3,600$ pg/ml	6	42.9
$> 3,600$ pg/ml	2	14.3
Vitreous TGF-β1 levels Without PRP Laser Therapy		
$\leq 3,600$ pg/ml	1	7.1

Table 2. Comparative Analysis of Serum and Vitreous TGF- β 1 Levels.

Variable	Laser History	n	Mean (pg/ml)	SD	p-value
Serum TGF- β 1	Yes	8	14,187.5	5,338.9	0.245
	No	6	11,000.0	4,987.6	
Vitreous TGF- β 1	Yes	8	3,587.5	352.3	0.104
	No	6	3,833.3	273.3	

The test is done with the Mann-Whitney test.

women can be inhibited by sex hormone receptors. The PDR development can be inhibited by inhibiting hormone receptors, although this mechanism is still unclear.¹⁵ Meanwhile, age above 50 years and a history of metabolic syndrome have been reported as one risk factors in the development of DM and PDR.¹⁶

The mean value of TGF- β 1 levels in patients with or without PRP laser therapy using a vitreous sample was $3,692.86 \pm 333.89$ pg/ml, while the mean serum level was $12,821.43 \pm 5,25$ pg/ml (Table 1). However, after treatment (Table 2), the vitreous TGF- β 1 level in the group treated with laser therapy showed lower values than patients who did not receive PRP laser therapy. In contrast, the serum samples showed higher values in patients that received PRP laser therapy. Consequently, it was concluded that the administration of laser therapy has a good effect in reducing the level of TGF- β 1 locally in the eye but has no significant effect systemically.¹⁷ Administration of PRP laser therapy improves the hypoxic state of the retina and the levels of cytokines in the vitreous fluid, thereby preventing proliferation and further neovascularization.¹⁸ Shimura et al. (2009) stated that PRP laser therapy before vitrectomy surgery could reduce levels of angiogenic factors such as VEGF, IL-6, and TGF β .¹⁹

TGF-1 is a polypeptide cytokine of the transforming growth factor-beta family. It is a secreted protein that regulates cell growth (cell cycle regulation and death), cell proliferation, cell differentiation, and tumor suppression.²⁰⁻²² TGF- β is released into the extracellular matrix as a latent protein complex integrated into a latency-associated protein and one of four TGF- β binding protein isoforms. TGF- β activation, which is necessary for biological activity, happens via poorly known mechanisms that most likely include proteolytic degradation of the related proteins and release of the TGF- β ligand. TGF- β 1 is the most common and widely expressed isoform; most researchers have explored or used exogenous TGF- β 1 as a biomarker variable.²³

It has been proposed that pericyte control of endothelial cell proliferation occurs by activating pericyte-secreted

latent TGF- β , which entails the proteolytic release of TGF- β from its binding protein. Furthermore, among the six known TGF- β subtypes, only TGF- β 1 is inhibitory for endothelial cells and only for particular kinds of endothelial cells.²⁴

The retina's oxygenation status controls different growth factors that induce angiogenesis to fulfill the tissue's oxygen demands. Sustained hyperglycemia caused by long-term diabetes causes many metabolic changes that contribute to retinal hypoxia. It would, however, promote some biomarkers such as insulin-like growth factor-I (IGF-I), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), endothelin (ET), pigment epithelium-derived factor (PEDF), and transforming growth factor- β (TGF- β).^{25,26}

TGF- β signaling is necessary for retinal pericyte differentiation during retinal vascular development. The absence of TGF- β signaling produces many microaneurysms, leaky capillaries, and retinal hemorrhages. Furthermore, the lack of differentiated pericytes begins a scenario of structural and functional alterations in the retina similar to those seen in diabetic retinopathy, indicating a related mechanism.²⁷

TGF- β is also a neuroprotective protein that contributes to the recovery from diverse neural damage. The activation of stress response proteins and the metabolic activity, such as aldehyde dehydrogenase 3A1 (ALDH3A1), heme oxygenase-1 (HO-1), nuclear factor erythroid 2-related factor (Nrf2), and hypoxia-inducible factor (HIF), was linked to TGF- β 1 mediated antioxidant signaling. It was also shown that TGF- β protects retinal ganglion cells (RGCs) from hyperglycemia-induced damage by activating the antioxidant system, implying a possible anti-diabetic therapy to treat diabetic retinopathy.²⁸

According to Zorena et al. (2013), the threshold serum TGF- β 1 values that showed a discriminative potential to predict the existence of DR were 443 pg/ml. It was determined by analyzing the receiver operating characteristic (ROC) curves. The computed sensitivity and specificity were 72% and 88%, respectively. TGF- β 1 serum concentrations may be

an additional criterion in predicting the incidence of DR, according to these findings.²⁹

Serum TGF- β 1 levels can be influenced by other factors such as hypertension and dyslipidemia.^{30,31} In conditions of hyperglycemia, TGF- β 1 levels also increase. These findings are in line with several other studies which stated that elevated levels of TGF- β 1 are also found in other systemic diseases such as diabetic nephropathy, lung and autoimmune diseases, cancer, cardiovascular disease, hyperglycemia, and hypercholesterolemia.^{20,32-34}

Moreover, there is also a correlation between laser burning and the duration of TGF- β 1 levels. Measurement of laser timing in a study by Xu et al. (2018) showed that after PRP laser therapy, TGF- β 1 levels in the vitreous return to normal in 3 weeks.³⁵ Previous studies also showed that laser burn ranging from 1,200-to 1,500 and a spot size of 500 μ m reduces oxygen demand outside the retina up to 20% and the levels of growth factors in the vitreous.³⁶ The number of burns in this range can be beneficial as it balances oxygen demand and availability to reduce hypoxic areas. Consequently, this lowers the levels of angiogenic factors, including TGF- β 1.^{37,38} Meanwhile, the number of burn calculations is expected to provide information about the effect of PRP laser therapy which is believed to prevent severe visual loss for up to 2 years after therapy.^{39,40}

CONCLUSION

Based on the results, there was no significant difference in serum and vitreous TGF- β 1 levels between subjects with and without PRP laser therapy. However, the trend of TGF- β 1 levels in subjects with PRP laser therapy was lower than in those without panretinal photocoagulation laser therapy.

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DISCLOSURE

Statement of Ethics

The Ethics Committee of Medical Research, Faculty of Medicine, Hasanuddin University, reviewed and approved this study protocol with approval number: 515/UN.4.6.4.5.31/PP36/2021.

Conflict of Interest Statement

The authors state there is no conflict of interest in writing this article.

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Data availability statement

Not applicable.

Author Contributions

HSM, RZA, AMI: conception or design of the work, performing the medical examination, analyzing and interpreting the data, laboratory examination and drafting the work. BD, JS: Supervise and quality check of the medical examination, care for patients and perform follow-up after surgery. AS, ICI: project administration, data statistic evaluation, drafting the work and final check for publication.

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