Majalah Kedokteran Sriwijaya
Th. 52 Nomor 3, Juli 2020

CORRELATION OF Hba1c LEVELS WITH PUPILLARY RESPONSE TO APRACLONIDINE 0,5% EYE DROPS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Devi Azri Wahyuni[1], Nafila Mahida Sukmono[1], Erial Bahar[2]

[1]Ophthalmology Department, dr. Mohammad Hoesin General Hospital Palembang, Faculty of Medicine, Sriwijaya University, Palembang
[2]Anatomy Department, Faculty of Medicine, Sriwijaya University, Palembang

Email: devi.syukriaf@yahoo.com

ABSTRACT

Pupillary reflex abnormalities can result from disorders of the innervation or iris structure of the eye. In people with diabetes mellitus, the pupil size becomes smaller than normal due to neuropathy in innocent sympathetic innervation of the pupil. This neuropathy is associated as a manifestation of uncontrolled diabetes complications. Pupillary response is associated as a general indication of autonomic neuropathy disorders in diabetes mellitus patients. Apraclonidine as an ophthalmic sympathomimetic agent can cause mydriasis, which is likely to identify pupillary sympathetic denervation in type 2 diabetes mellitus patients. This study aimed to find out the correlation between HbA1c levels and pupillary response to 0.5% Apraclonidine eye drops in diabetes mellitus type 2 patients at Mohammad Hoesin Hospital Palembang. Observational research with a correlation test design to investigate the correlation of HbA1c levels with pupillary response to apraclonidine 0.5% eye drops in patients with type 2 diabetes mellitus has been conducted from March to May 2019. The study sample met the inclusion and exclusion criteria of 31 diabetics mellitus type 2 with HbA1c level> 6.5% in the Eye clinic at the Mohammad Hoesin Palembang hospital. In this study 31 patients with type 2 diabetes mellitus with HbA1c levels >6.5 mg% were obtained. The average HbA1c level was 9.5 ± 1.4 mg%, which ranged from 7.6 - 12.6 mg%. The glycemic status of the patients in this study were all (100.0%) in an uncontrolled condition (HbA1c> 7.5 mg%). The estimated duration of diabetes mellitus is 2.7 ± 1.8 years, with a minimum value of 1 year and the largest being 8 years. The average change in pupillary diameter before - after dropping 0.5% apraclonidine was 1.16 ± 1.06 mm, ranging from 0 - 4 mm. There were 9 (29.0%) eyes that did not show any changes. Significant enlargement of pupillary size after dropping 0.5% apraclonidine (p = 0,000). This change in pupil size correlated with the estimated duration of diabetes mellitus (r = 0.436, p = 0.014) and HbA1c levels (r = 0.492, p = 0.005). Pupil size after using 0.5% apraclonidine has a distribution value of 4 (3-6) mm can be interpreted that there are subjects who have no change, but there are patients who have pupils dilated to 6 mm.

Keywords: Pupillary response, Diabetes Mellitus complication, HbA1c

1. INTRODUCTION

Pupils are one of the eye organs that function to deliver light. Pupils will widen in dark room conditions and shrink when the room is bright. Pupil size is influenced by several factors including age, level of consciousness, strong irradiation, and level of accommodation. Changes in pupillary diameter are affected by sympathetic and parasympathetic fibers in the efferent pathway. The function of the sympathetic nerve is dilation of the pupil with a less significant effect on the ciliary muscle,

whereas the parasympathetic nerve functions for ciliary muscle contraction and the effect of accommodation. Thus, the pupillary diameter is determined by the antagonistic action of the pupillary sphincter and the dilator pupillary musculature. [1,2]

Directly or indirectly irradiating, the pupil normally experiences constriction called the pupillary reflex miosis. This constriction of the pupil aims to provide greater depth of focus because far and near objects are focused at the same time, and also to reduce all distortions produced by the lens. [1,2] Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia that occurs due to abnormal insulin secretion, insulin performance or both. Basic Health Research shows a significant increase in the prevalence of DM, from 6.9% in 2013 to 8.5% in 2018; so the estimated number of people with DM in Indonesia reaches more than 16 million people who are then at risk of other diseases, such as: heart attack, stroke, blindness and kidney failure can even cause paralysis and death.

According to WHO, DM is defined as a disease or chronic metabolic disorder with multi-etiology characterized by high blood sugar levels accompanied by impaired carbohydrate, lipid and protein metabolism as a result of insulin function insufficiency. According to data from the Palembang city health office, DM was ranked 8th in the list of 10 most diseases in 2017. It was later discovered that beta cell failure occurred earlier and was more severe than previously thought. In addition to muscle, liver and beta cells, other organs such as: fat tissue (increased lipolysis), gastrointestinal (incretin deficiency), alpha pancreas cells (hyperglucagonemia), kidneys (increased glucose absorption) and brain (insulin resistance), all of which play a role in causing the occurrence of impaired glucose tolerance in DM type. [2.3,4]

The diagnosis of DM must be based on checking blood glucose concentration. In determining the diagnosis of DM must be considered the origin of blood material taken and the method of examination used. One of the tests is the HbA1c examination which has been used as a diagnostic and monitor check in DM cases. Hemoglobin a1c (HbA1c) was initially identified as "unusual" hemoglobin in diabetic patients for 40 years and the HbA1c examination gave an indication of chronic glycemic events compared to being a glycemic test tool at one time.[5,6]

Persistent hyperglycemia is considered a primary factor in diabetic neuropathy. This metabolic factor is not the only one responsible for the occurrence of diabetic neuropathy. There are other theories that are accepted, namely vascular theory, autoimmune and nerve growth factor. Some say that besides the role of glycemic control, the incidence of neuropathy is also associated with potential cardiovascular risks that can still be modified. ND manifestations can vary greatly, ranging from no complaints and can only be detected by electrophysiological examination, to severe pain complaints. It can also be a complaint in the form of local or systemic neuropathy, which all depends on the location and type of nerve affected by the lesion. [4-6] Neuropathy occurs in 7.5% of patients diagnosed with DM. More than half are distal symmetrical polyneuropathies. There is no racial predilection specifically for diabetic neuropathy. But black people are more likely to develop secondary complications from diabetic neuropathy, such as amputations of lower extremity than white people. DM regarding both men and women alike. However, male patients with type 2 diabetes can develop polyneuropathy earlier than women. Diabetic neuropathy is usually more common in the elderly.[4,6]

Pupils are a good place to get information about the state of diabetic autonomic neuropathy because the innervation of pupils is exclusively autonomous and easily accessible for research without causing discomfort to the patient. In the study of A. Smith and S. E.

Smith, it was mentioned that type 2 DM patients had smaller pupil sizes than normal ones it may be due to neuropathy in innate sympathetic pupillary dilator so that pupillary reflex examination can be used to diagnose early diabetic neuropathy. In diabetic neuropathy patients, iris is often found damaged with lesions found in smooth muscle, connective tissue and blood vessels. Suggests other etiologies for small pupils such as local damage to the iris that inhibits iris movement. Another etiology is by conducting a pupillary response study with topical sympathometic administration in diabetic patients with or without small pupils.

In the study of Fion D. Bremner and Stephen E. Smith mentioned that in general, pupils in patients with type 2 DM myosis, especially when it is dark. In a screening study, 21.7% of 359 type 2 DM patients found abnormal small pupillary sizes. The relationship between small pupil size and diabetes complications has been noted in several studies, such as the correlation with cardiovascular autonomic disorders mentioned in the study of Smith et al. In Heridarsson's research it was mentioned the relationship between small pupillary size and severe and chronic hyperglycemia. In one study mentioned, severe miosis was also found to be associated with supersensitivity to phenylephrine.[3] In the Koc study, F et al found a similarity in sensitivity and specifications of 0.5% apraclonidine with topical cocaine to enforce Horner's syndrome. Topical 0.5% apaclonidine was found to have a dilating effect on pupils of Horner's syndrome patients. [3-5]

HbA1c examination has become a diagnostic examination for cases of type 2 diabetes. HbA1c examination results provide an indication of chronic glycemic in DM type 2 patients. Thus, suspected in cases of DM with high levels of HbA1c consistency can also occur diabetic neuropathy. The application of 0.5% apraclonidine eye drops in the Koc F et al study provided pupillary responses in patients with Horner's syndrome who were found to have abnormalities in the sympathetic nerve pathway. This study aimed to find out about the correlation of HbA1c levels with pupillary response to 0.5% Apraclonidine eye drops in patients with type 2 DM Mohammad Hoesin Hospital Palembang. The aim of this research is to determine the correlation of HbA1c levels with pupillary response to apraclonidine 0.5% eye drops in type 2 DM.

2. METHOD

This study was an observational study with a correlation test design to investigate the correlation of HbA1c levels with pupillary response to apraclonidine 0.5% eye drops in patients with type 2 diabetes mellitus. This research was conducted at the hospital. Mohammad Hoesin Hospital Palembang between the period January 2019 to March 2019.

The study sample was people with type 2 diabetes mellitus fulfilling the inclusion and exclusion criteria. In this study the sampling technique used was consecutive sampling. The inclusion criteria in this study are (a) Type 2 diabetes mellitus willing to participate in research that fills out and signs informed consent. While the exclusion criteria are if the patient has (a) History of glaucoma disease (b) History of use of anti-glaucoma eye drops (c) History of intraocular surgery (d) Are suffering from acute external eye infections and intraocular inflammation (e) Using contact lenses.

All data is displayed in the form of tabulated data and performed statistical analysis using a computer program with the SPSS program. All variables in this study were analyzed univariately presented in the form of frequency distribution tables and narratives. while the correlation test used is the Spearman test.

3. RESULT

In this study the dominant age distribution around 50-60 years was 17 (54.8%) subjects, age> 60 years there were 11 (35.5%) subjects and 40-50 years were 3 (9.7%). More male subjects than female subjects were actually 19 (61.3%) showed in Table 1.

Table 1. Characteristic of Subject

Characteristic	Frequency (n)	Percent (%)
Age		
40-50 years	3	9.7
50-60 years	17	54.8
>60 years	11	35.5
Sex		
Male	19	61.3
Female	12	38.7
HbA1c	9.51% ± 1.4 %	
Duration of DM	2 (1-8) years	
Pupil Size Before Using Apraclonidine 0.5%	3 (3-3) mm	
Pupil Size After Using Apraclonidine 0.5%	4 (3-6) mm	
Size of pupillary enlargement before and after using Apraclonidine 0.5%	10 (0-4) mm	

*Normally distributed data are presented with mean ± standard deviation (SD), and abnormally distributed data are presented with a median (minimum-maximum)

Bivariate correlation test analysis uses Spearman's Rho. There a significant correlation between pupillary size after the use of 0.5% apraclonidine and pupillary enlargement with HbA1c levels with moderate correlation. There is no significant relationship between duration of DM with HbA1c levels. can be seen in Table 4.3. There was a very significant relationship (p = 0,000) between pupil size after using 0.5% apraclonidine and pupillary enlargement with strong correlation strength (r = 1,000). And there is a significant relationship (p = 0.014) between the duration of DM with moderate correlation (can be seen in Table 2).

Table 2. Analysis of pupillary response correlations with HbA1c levels

	Kadar HbA1c
Pupil Size After Using Apraclonidine 0.5%	p = 0.005 r = 0.492
Size of pupillary enlargement before and after using Apraclonidine 0.5%	p = 0.005 r = 0.492
Duration of DM	p = 0.064 r = 0.337

*Spearman's rho correlation test, significant value P <0.05, correlation strength value is very low if 0 - 0.199, correlation value is low if 0.20-0.39, moderate if 0.40 - 0.599, strong correlation value if 0.60- 0.799 and very strong if 0.80-1.00.

Table 3. Correlation analysis Pupil size after the use of 0.5% Apraclonidine with pupillary enlargement and duration of DM

	Pupil Size After Using Apraclonidine 0.5%
Size of pupillary enlargement before and after using Apraclonidine 0.5%	p = 0.000 r = 1.000
Duration of DM	p = 0.014 r = 0.436

*Spearman's rho correlation test, significant value P <0.05, correlation strength value is very low if 0 - 0.199, correlation value is low if 0.20-0.39, moderate if 0.40 - 0.599, strong correlation value if 0.60- 0.799 and very strong if 0.80-1.00.

4. DISCUSSION

This study aims to see changes in the size of the right eye pupils from before dropping 0.5% apraclonidine with 60 minutes after dropping. Apraclonidine is an ophthalmic sympathomimetic agent pharmacologically belonging to the α2 agonist group and although weaker it is also an α1 agonist. Apraclonidine in 0.5% and 1% solutions has long been used clinically. 1% solution is used to control or prevent increased postoperative intraocular pressure (IOP). Apraclonidine 0.5% is also used as a short-term adjunct agent to reduce IOP in glaucoma patients receiving maximum tolerated medical therapy. This drug was approved by the FDA in 1987.31 For diagnostic purposes in the field of neuroophthalmology, apraclonidine has long been used to diagnose or confirm Horner's syndrome replaces cocaine solution which is more difficult to get.[7-9] In this study 31 patients with type 2 DM with HbA1c levels> 6.5 mg% were obtained. The average HbA1c level was 9.5 ± 1.4 mg%, which ranged from 7.6 - 12.6 mg%. The glycemic status of the patients in this study were all (100.0%) in an uncontrolled condition (HbA1c> 7.5 mg%). The estimated duration of DM is 2.7 ± 1.8 years, with a minimum value of 1 year and the largest being 8 years.

Important findings in this study can be summarized as follows:

a. Pupillary diameter in DM patients is 3 mm (before apraclonidine 0.5%).
b. Pupil diameter of 60 minutes after drops of 0.5% apraclonidine is 4.16 ± 1.06 mm, which ranges from 3-7 mm.
c. The average change in pupillary diameter before - after dropping 0.5% apraclonidine is 1.16 ± 1.06 mm, ranging from 0-4 mm. There were 9 (29.0%) eyes that did not show any changes.
d. Significant enlargement of pupillary size after 0.5% apraclonidine drop (p = 0.000)
e. This change in pupil size correlates with the estimated duration of DM (r = 0.436, p = 0.014) and HbA1c levels (r = 0.492, p = 0.005).

The pupil size of the patient before being given a 0.5% apraclonidine drop was obtained by 3 mm in the right eye of all the patients examined. This pupil size is still normal for adults, but in this study, we have no evidence whether this pupil size is smaller than the pupil size of patients before suffering from DM. In previous studies it was found that pupillary abnormalities in DM sufferers most often found are pupillary miosis. Other research also found a negative correlation between pupil size and duration of DM, the longer a person has DM the smaller the pupil

size.[10,11] The most likely explanation for explaining the correlation between DM duration and myotic pupillary size, is due to denervation of the sympathetic nervous system in patients with DM, so that the amount of norepinephrine is not enough to trigger α1 receptors on the pupillary nerve.

In general, normal pupillary size in adults ranges from 2 to 4 millimeters (mm) in diameter in bright light to 4 to 8 mm in the dark.[2,3] Pupillary size in general can be said to be the resultant between sympathetic nervous system tone and nervous system parasympathetic to iris muscles. Pupil size depends on the intensity of the incoming light and the integrity of the components involved in the light reflex arch; 1) retina (receptor), 2) n.optikus (afferent fibers), 3) superior coliculus (center of light reflex), 4) autonomic system (efferent) 5) m.constrictor pupillae and m. pupillary dilator (effector).[3,5-12] The parasympathetic system that supplies the eye originates from the nc.Edinger Westphal in the mesensefalon region whose fibers run in the nococomotorius (n.III) and travel to the ciliary ganglion to influence the accommodation function (m.ciliaris), secretion of the aquatic gland (ciliary gland) and consecration. pupil (m. constrictor pupillae). The parasymphatic nerve endings release acetylcholine as a neurotransmitter.[7,12]

The symphatic system leading to the eyeball (oculosympathetic pathway) consists of a series of 3 neurons; first order neurons located in the hypothalamus, receive input from superior coliculus and send descending fibers to the thoracic intermediolateral horn (order II neurons), fibers from order II neurons are called praganglionic fibers, using acetylcholine as neurotransmitters travel to the symphatic intermediate caudal ganglion (neurons of order II), fibers from order II neurons are referred to as praganglionic fibers, using acetylcholine as neurotransmitters traveling towards the symphatic intermediate caudal ganglion (neurons of order II), fibers from order II neurons referred to as praganglionic fibers, using acetylcholine as neurotransmitters traveling towards the symphatic intermediate caudal ganglion (neurons of order II). III). Fibers from the superior cervical ganglion, called postganglionic fibers, travel together and follow the distribution of branches of the external and internal carotid arteries, one of which ends in the pupillary and corpus ciliary branches. Symphatic postganglionic fibers secrete norepinephrine as an adrenergic neurotransmitter.[7,12]

In this study it was found that the majority of pupils (in 22 patients = 71.0%) experienced an increase in pupil size and in 9 patients (29.0% found no change. Enlargement of pupil size that occurred had a median of 1 mm (ranging between 0 mm and 4 mm). Statistical analysis using the Wilcoxon test showed a significant increase in pupil size (p = 0,000), after 60 minutes a 0.5% apraclonidine drop was applied.

Spearman correlation analysis found a significant correlation between the increase in pupil size after 60 minutes of dropping 0.5% apraclonidine with HbA1c levels (r = 0.492, p = 0.005) and with the estimated duration of DM (r = 0.436, p = 0.014). In the multiple linear regression analysis, there was no effect of the age or gender of the patient on the change in size. To explain the correlation mechanism between increasing pupil diameter size and HbA1c levels and duration of DM, an analogy was examined using Horner's syndrome as a reference. The use of apraclonidine eye drops in Horner's syndrome has been widely reported. In Horner's syndrome, there is denervation of sympathetic nerve fibers in the oculo-sympathetic pathway resulting in pupillary anisocoria symptoms, ptosis and skin anhidrosis on the affected side. Reduced adrenergic stimulation of the pupillary m. dilator causes the pupil size to shrink (miosis). In an effort to compensate the body increases the number (up-regulation) of α1 receptors in the muscle cells of the pupillary muscle, making them hypersensitive to adrenergic stimulation. Under hypersensitive conditions such as the

dropping of apraclonidine will trigger the pupillary muscle fibers resulting in enlargement of the pupil size, this condition is referred to as a positive apraclonidine test. Clinically seen as a loss, reduction of anisokoria or anisokoria reversal (from miosis to mydriasis). Some researchers report that in normal people, drops of apraclonidine solution in the eye do not cause mydriasis. [8,13]

In patients with DM also possible denervation in the oculo-sympathetic pathway leading to the eyeball. Decreased adrenergic (norepinephrine) stimulation of α1 receptors in the smooth muscle cells of the pupillary millillator is followed by compensatory efforts by up-regulation of α1 receptor protein expression. Increasing the number of postjunctional α1 receptors causes increased sensitivity of the pupillary muscle fibers response to apraclonidine 0.5%.

In general, adrenergic receptors are distinguished in 1) receptor α1 receptor, excitatory, β1 receptor (excitatory) and β2 receptor (inhibitory) and 2) prejunctional: α2 receptor, inhibitory to norepinephrine or acetylcholine secretion. The number of α1 receptors is far more than α2, so that in normal circumstances the release of norepinephrine in the iris will trigger the contraction of the m.dilator pupillae and the relaxation of the m.constrictor pupillae, resulting in mydriasis.[8,14] In iris, apraclonidine is an agent that is agonizing (triggering) prejunctional α2 receptors and although weak is also an agonist for α1 receptors. Under normal conditions, drops of apraclonidine do not cause significant changes in pupillary diameter in both dark and light conditions.[14] In the state of oculosympathetic pathway denervation, as seen in Horner's syndrome, various studies have shown that apraclonidine can cause mydriasis. The main symptoms of Horner's syndrome are anisochorous pupils, ptosis and facial skin anhidrosis on the affected side. All of these symptoms are caused by damage (denervation) in the oculosympathetic pathway which causes not enough norepinephrine to trigger α1 receptors and contraction of the m.dilator pupillae, while the parasympathetic pathway that triggers contraction of the m.constrictor pupillae is not disturbed so as a result there is a myosis of the problematic side eye.[3,5,6]

The bad effects of DM on nerve fibers have been widely studied. Various pathomechanisms have been proposed to explain the occurrence of diabetic neuropathy, but simply the adverse effects due to DM stem from only 2 mechanisms, namely the adverse effects of prolonged hyperglycemia (glucotoxicity effect) and the adverse effects due to disruption of fat metabolism (lipotoxic effect). The longer a DM sufferer has uncontrolled hyperglycemia, the greater the impact of glucotoxicity and lipotoxic damage. Diabetic neuropathy in diabetics may occur in the form of somatosensory neuropathy, autonomic neuropathy or in a combination of both. autonomous to the system cardiovascular, nervous, reproductive, gastrointestinal and so on. DM affects the sympathetic nervous system and parasympathetic nerves, but the administration of apraclonidine 0.5% eye drops only affects the sympathetic nerve. This research can only answer the possibility of sympathetic denervation in type 2 DM.

5. CONCLUSION

There was a significant correlation (p = 0,000) between sizes pupils after using 0.5% apraclonidine with enlargement pupils with a very strong correlation strength (r = 1,000). This study found that there was a correlation between HbA1c levels and pupillary response to 0.5% apraclonidine eye drops in type 2 diabetes mellitus, so that it could help as an early warning of possible sympathetic pupillary denervation. For further studies can use 0.5% apraclonidine in detecting pupillary abnormalities in patients with type 2

diabetes mellitus controlled. It is recommended for further research to use pupillary measurements with pupillometry to achieve better accuracy and eliminate research bias.

REFERENCES

[1]. American Academy of Ophthalmology. Basic and Clinical Science Course Neuro-Ophthalmology, 2016-2017. Copyright ©2016. American Academy of Ophthalmology. All rights reserved.
[2]. Sadun A. Anatomy and Physiology, Neuro-Ophthalmology, The Afferent Visual System. 9:2 Downloaded from ClinicalKey.com by Elsevier on September 04, 2018. Copyright ©2018. Elsevier Inc. All rights reserved.
[3]. Levin L, et al. Adler's Physiology of the Eye, Regulation of light through pupil; Eleventh Edition, 2011. 25: Copyright ©2011. Elsevier Inc. All rights reserved.
[4]. Hasil utama riskesdas tahun 2018 kementerian kesehatan badan penelitian dan pengembangan kesehatan.
[5]. Remington LA. Uvea, in Clinical Anatomy of the Visual System. Copyright ©2015. Elsevier Inc. All rights reserved.
[6]. Al Arouj M, et al. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Copyright ©2011, WHO Press. All rights reserved.
[7]. Daroff R, et al. Bradley's Neurology in Clinical Practice, Chapter 45. Seventh Edition. Copyright ©2016, Elsevier Inc. All rights reserved. Downloaded from ClinicalKey.com by Elsevier on August 09, 2018.
[8]. Morales J, Brown SM, Abdul-Rahim, et al. Ocular effects of apraclonidine in Horne syndrome. Arch Ophthalmol. Copyright© 2000.
[9]. Gharagozloo NZ. Aqueous flow is reduced by the alpha-adrenergic agonist, apraclonidine hydrochloride. Ophthamology. Copyright©1988.
[10]. Hartanto, dkk. Patofisiologi Konsep Klinis Pankreas: Metabolisme Glukosa dan Diabetes melitus. Proses-Proses Penyakit (Sylvia A. Price & Lorraine M. Wilson). Edisi 6. Copyright © 2003 FK UI. Jakarta
[11]. Braziz PW, Maedeu JC. The localization off lession in oculomotor system, in localization in the clinical neurology. Copyright © 1990. Little Brown. London.
[12]. Florkowski C. HbA1c as a Diagnostic Test for Diabetes Mellitus – Reviewing the Evidence. Clinical Biochemistry. Copyright ©2013, Elsevier Inc. All rights reserved.
[13]. Iopidine (apraclonidine 1%) package insert. Fort Worth, TX: Alcon Laboratories, Inc. Alcon. Copyright© 2018
[14]. Fukashi I. Et al. The Preferential Impairment of Pupil Constriction Stimulated by Blue Light in Patients with Type 2 Diabetes without Autonomic Neuropathy. Downloaded from Hindawi Journal of Diabetes Research on August 14, 2018.