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Comparison of Retinal Nerve Fiber Layer Structures and Macula Thickness in Opioid Dependent and Normal Adult

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Abstract

Introduction: Heroin and morphine, which falls under the opioid group continues to be the commonest drug of abuse in Malaysia. Opioid usage is associated with addiction and dependence, and reported ocular side effects are pupillary miosis, conjunctiva hyperemia, ocular motility disorder and risk of complication such as endophtalmitis. It was also reported that chronic opioid usage leads to neurological degeneration.

Objective: To compare the retinal nerve fiber layer thickness, macula thickness and optic nerve head parameters in opioid dependent and normal adult.

Method: In this study design was a case control with opioid dependent individuals and healthy individuals recruited from the Methadone Clinic, Department of Psychiatry and Ophthalmology Clinic, Department of Ophthalmology, Hospital Universiti Sains Malaysia. Thirty five opioid dependent subjects and thirty five healthy subjects with no history of opioid use were recruited. Ophthalmological examination and optical coherence tomography (Heidelberg Spectralis® OCT) were performed.

Results: Compared to normal healthy subjects, opioid dependent group has thinner average retinal nerve fiber layer in the right eye ($p<0.05$) and in superior quadrant of optic nerve ($p<0.05$). Analysis of other segments did not show any statistical significance

Conclusion: Early thinning of the retinal nerve fiber layer could be one of the early signs of complication from long term opioid usage. Further studies may be needed to determine if further thinning occurs in time and the implication to the patient's vision.

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Introduction

Opioid is a generic term used to describe opiates and their synthetic analogues [1]. Opioid substance binds to opioid receptors to create agonist, partial agonist and antagonist effects [2]. They are infamously reputed for their use in abuse and addiction. However, some of it has their usage in medical therapy.

Opioid can be classified according to their origins which are either natural derived, semi-synthetic or synthetic compound. Natural derived from opium poppy includes morphine and codeine while semi-synthetic types are heroin, oxycodone and buprenorphine. Synthetic opioids are methadone, pethidine and fentanyl. Opioid acts on different types of opioid receptors found in our body. Based on International Union of Pharmacology, the four subtypes of opioid receptors are MOP (mu), KOP (kappa), DOP (delta) and NOP.

Based on 2014 statistics provided by the Malaysian National Anti-Drug Agency (AADK), there were a total of 21777 illicit drug users whereby 13605 of them were newly detected users. Of the types of drugs usage reported, heroin and morphine comprises 64.9%, followed by methamphetamine at 18.4% and cannabis 8.6%. The primary route of administration for both heroin and morphine was "chasing the dragon" (72.2%) compared to by injecting (8.5%). Users are common to mix other drugs besides usage of opioids to maximize the euphoric effects, possibility due to increase in tolerance and also reportedly reduced in purity of heroin obtained [3].

Opioid causes effects of sedation, analgesia and especially heroin usage leads to euphoria, which was the primary aim for drug abusers. There are also undesirable side effects such as nausea, vomiting, respiratory depressant, urinary retention, constipation, physical dependence and tolerance.

A few reported ocular side effects from systemic administration of heroin are pupillary miosis and unreactive pin-point appearance in toxic state, conjunctiva hyperemia, internuclear ophthalmoplegia and nystagmus. Following heroin withdrawal, there were reports of patients having excessive tearing, anisocoria, strabismus and ocular motility disorders [4,5]. Other known complications as an effect from intravenous injection includes bacterial and fungal endophthalmitis.

Chronic heroin abusers have been shown to develop structural brain changes which could have been from primary cause of heroin or from additional substance used as adulterant. The changes reported includes cerebral atrophy, area of demyelination in white matter and decreased neuronal density [6-8]. With the retina and optic nerve as the extension of the brain [9], our current study is to determine if there are any changes seen in the retina nerve fiber layer due to chronic opioid usage.

Methods

Subjects

The study was approved by the Research and Ethical Committee, School of Medical Sciences, Universiti Sains Malaysia on 10th February 2014. This study was carried out in accordance to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

All participants provided written informed consent before inclusion in the study. The study design was a case control with opioid dependent individuals and healthy individuals recruited from the Methadone Clinic, Department of Psychiatry and Ophthalmology Clinic, Department of Ophthalmology, Hospital Universiti Sains Malaysia.

Opioid dependent individuals who attended the Methadone Clinic were invited to participate in the study. Inclusion criteria for the opioid dependent group (n=35) were individuals with history of heroin or morphine and methadone use for at least 12 months, clear ocular media at time of examination and age of above 18 years. The exclusion criteria were known clinical history of stroke, neurological or demyelinating disease, previous ocular history of trauma or surgery, optic neuropathies such as glaucoma and optic neuritis, hereditary or acquired retinopathy and maculopathy and refractive error of spherical equivalent of more than 4 dioptres.

As for the healthy control groups (n=35), they were recruited from individuals who had responded to the "Control Group Recruitment Advertisement" and fulfilled the selection criteria. Inclusion criteria were healthy individuals with no history of any substance usage especially opioids group, clear ocular media and age of above 18 years. The exclusion criteria were history of substance abuse, known clinical history of stroke, neurological or demyelinating disease, previous ocular history of trauma or surgery, optic neuropathies such as glaucoma and optic neuritis, hereditary or acquired retinopathy and maculopathy and refractive error of spherical equivalent of more than 4 dioptres.

Ophthalmological assessment

Ophthalmological assessment included measurement of Uncorrected Visual Acuity (UCVA) and "Best at Presentation" Visual Acuity (BAPVA) using Snellen Visual Acuity Chart. BAPVA was determined by using pinhole. Intraocular pressure was measured using Reichert Tono-Pen® tonometer. Slit lamp examination was performed to examine the anterior and posterior segment to document any detected pathology.

Optical coherent tomography (OCT)

RNFL average at the optic disc and RNFL thickness of the quadrants of optic nerve head were measured using Heidelberg Spectralis® OCT (Heidelberg Engineering, Heidelberg, Germany). The scan centered at the optic disc was automatically acquired. The Spectralis OCT software version 6.0.14 was used for automatic generation of the quadrants of the optic nerve head, which were superior, inferior, nasal and temporal quadrant.

Macular thickness was measured using Heidelberg Spectralis® OCT, with the "6mm fast macular mapping" scanning pattern protocol. A good quality macular mapping of the posterior pole with the fovea as the central locus was taken. Quality of at least 25 in the quality bar was accepted for analysis. Both procedures of handling the OCT for measurement was taken by trained medical personnel. Data showing the central macular thickness was used for data analysis.

Statistical analysis

All statistical analysis and data entry was done using Statistical Package for Social Sciences software version 22.0 (SPSS Inc, IBM, New York, USA). Mean values and standard deviation were used for descriptive analysis.

Values for the RNFL, optic nerve head quadrants and macular thickness were tested for normality and model assumption. Analysis of Covariance (ANCOVA) was used to compare the retinal thickness, quadrant RNFL and macular thickness between the opioid dependent group and control group, while control-

ling for age. Statistical significance was reported at p<0.05.

Sample size and sampling

Sample size calculation was derived using PS Software – Power and Sample Size calculation version 3.0.43 using t-test formula.

Calculation done to detect a mean difference between the two groups difference in RNFL thickness of 5 µm with a standard deviation ± 10.14µm [10] and a standardised difference of 0.50, results in a sample size of 35 opioid dependence subjects and 35 controls. This would achieve an 80% probability of detecting differences between two group with p<0.05.

Results

The opioid dependent group consists of 35 subjects with similar number in the normal healthy control. This was the results of convenient sampling recruitment of normal subjects who had responded to the "Recruitment Advertisement". The demographic data for both groups are shown in Table 1.

The mean age group for opioid dependent were 38.6 ± 6.4 compared to healthy control 29.7 ± 6.9. There was statistical difference (p<0.001) in the mean age group. Analysis of Covariance (ANCOVA) was used to control the age confounding factor for subsequent analysis of the retinal thickness, quadrant RNFL and macular thickness between the opioid dependent group and control.

The mean retinal nerve fiber layer thickness between opioid dependent and healthy control were analysed using ANCOVA, adjustment with age. The results are shown in Table 2.

The mean difference in the RNFL between control and opioid dependent group were found to be statistically significant after controlling for age in OD retina average (adjusted mean 97.37 vs 104.63, p=0.015), OD superior quadrant (adjusted mean 118.42 vs 132.78, p=0.001) and OS superior quadrant (adjusted mean 123.02 vs 138.38, p<0.001). Analysis of other segments did not show any statistical significance.

Table 1: Demographic group.

	Control n=35	Opioid dependent n=35	p
Age (years)	29.7 ± 6.9	38.6 ± 6.9	<0.001[a]
Gender (n,%) Male	35 (100.0)	35 (100.0)	
Ethnic (n, %) Malay	35 (100.0)	35 (100.0)	
OD Uncorrected Visual Acuity (UCVA), (n,%)			
6/6	27 (77.1)	18 (51.4)	
6/7.5 - 6/12	5 (14.3)	12 (34.3)	
>6/18	3 (8.6)	5 (14.3)	
OS Uncorrected Visual Acuity (UCVA), (n,%)			
6/6	26 (74.3)	20 (57.1)	
6/7.5 - 6/12	7 (20.0)	10 (28.6)	
>6/18	2 (5.7)	5 (14.3)	
OD Best Corrected Visual Acuity (BCVA)M (n,%)			
6/6	31 (88.6)	29 (82.9)	
6/7.5 - 6/12	4 (11.4)	6 (17.1)	
>6/18	0 (0)	0 (0)	
OS Best Corrected Visual Acuity (BCVA)M (n,%)			
6/6	32 (91.4)	30 (85.7)	
6/7.5 - 6/12	3 (8.6)	5 (14.3)	
>6/18	0 (0)	0 (0)	
OD IOP (mmHg)	14.74 ± 2.3	13.7 ± 2.4	0.022[a]
OS IOP (mmHg)	14.8 ± 2.2	13.1 ± 2.2	0.002[a]
OD Cup-disc-ratio	0.38 ± 0.1	0.41 ± 0.1	>0.05[a]
OS Cup-disc-ratio	0.39 ± 0.1	0.42 ± 0.1	>0.05[a]
Coexist disease (n,%)			
HIV	0	6 (17.1)	
Hepatitis B	0	3 (8.6)	
Hepatitis C	0	26 (74.3)	
Hypertension	1 (2.9)	3 (8.6)	
Diabetes Mellitus	2 (5.7)	1 (2.9)	

Table 2: Retinal Nerve Fiber Layer Thickness Between Control and Opioid Dependent.

RNFL thickness (microns)	n	Adj. Mean (95% CI)[a]	Adj. Mean diff. (95% CI)[b]	F-stat (df)	P value
OD Whole Retina					
Control	35	104.63 (100.85, 108.42)	7.26 (1.40, 13.09)	6.19 (1,70)	0.015
Opioid	35	97.37 (93.59,101.16)			
OD Macula Thickness					
Control	35	272.42 (265.25,279.58)	9.2 (-1.83,20.23)	2.77 (1,70)	0.101
Opioid	35	263.21 (256.05,270.38)			
OD Superior					
Control	35	132.78 (127.33,138.23)	14.36 (5.97,22.75)	11.68 (1,70)	0.001
Opioid	35	118.42 (112.97,123.87)			
OD Inferior					
Control	35	135.16 (128.67,141.65)	8.89 (-1.10,18.87)	3.15 (1,70)	0.08
Opioid	35	126.27 (119.78,132.76)			
OD Temporal					
Control	35	73.28 (69.02,77.54)	-1.99 (-8.54,4.57)	0.37 (1,70)	0.55
Opioid	35	75.27 (71.01,79.52)			
OD Nasal					
Control	35	77.42 (71.56,83.27)	7.8 (-1.21,16.81)	2.99 (1,70)	0.089
Opioid	35	69.61 (63.76,75.47)			
OS Whole Retina					
Control	35	103.47 (99.60,107.34)	3.5 (-2.45, 9.46)	1.38 (1,70)	0.244
Opioid	35	99.96 (96.09,103.83)			
OS Macula Thickness					
Control	35	273.09 (266.20,279.98)	9.77 (-0.83,20.38)	3.38 (1,70)	0.07
Opioid	35	263.31 (256.42,270.20)			
OS Superior					
Control	35	138.38 (133.33,143.44)	15.37 (7.59,23.15)	15.53 (1,70)	<0.001
Opioid	35	123.02 (117.96,128.07)			
OS Inferior					
Control	35	132.63 (125.85,139.42)	3.24 (-7.20,13.68)	0.38 (1,70)	0.538
Opioid	35	129.4 (122.61,136.18)			
OS Temporal					
Control	35	72.27 (68.35,76.20)	1.95 (-4.10,7.99)	0.413 (1,70)	0.522
Opioid	35	70.33 (66.40,74.25)			
OS Nasal					
Control	35	70.42 (64.34,76.49)	-6.25 (-15.61,3.10)	1.78 (1,70)	0.187
Opioid	35	76.67 (70.59,82.75)			

Discussion

In the demographic table, all patients recruited from both groups are males and of Malay ethnicity. All subjects that were on methadone maintenance therapy at the Methadone Clinic were males. Based on Malaysian National Anti-Drug Agency 2014 statistics, males comprises of 96.8% of all recorded drug addicts [11]. Our sample collection of 100% Malay ethnicity does not represent any significance but is due to coincidence of sample collection. The study was conducted in the state of Kelantan where Malay ethnicity comprises of the majority of races.

As far as we know, there was no other similar study that compares thickness of the RNFL in any opioid users. Our results showed a few unexpected results. Differences in RNFL thickness between opioid dependent group and control were seen in the OD whole retina ($p<0.05$) but not in OS ($P>0.05$). This was unexpected as we predicted changes to occur bilaterally in systemic cause. We can only infer that there is asymmetry in the rate of deterioration.

Comparing of macular thickness in both groups does not show statistical differences. As the RNFL layer is thicker at the macula, the damage from opioid effects may be subtle.

RNFL of the optic nerve head shows statistical difference in

the superior quadrant of both eyes but not in other quadrants. Thinning of the superior quadrant shown in both eyes may signify early damages to the retinal nerve fiber layer due to chronic exposure to drug abuse. Anatomical study shows that the retinal nerve fiber layers are thickest inferiorly followed by superior rim. The inferior and superior rim are prone to early damage in glaucomatous changes due to the lamina cribrosa structure which has larger pores and thinner connective tissue and glial support for passing retinal ganglion cell axons [12,13]. We hypothesize that the reason thinning occurs in the RNFL is due to accumulated toxicity effect from substance abuse instead of the common risk factors of glaucomatous changes. In our demographic data, there was statistically difference between IOP for control and opioid user. Opioid users IOP was lower than control group (13.7 ± 2.4 vs 14.74 ± 2.3). The Cup-disc-ratio differences between two groups were not statistically difference. Experimental studies have shown morphine induced reduction of intraocular pressure [14,15], therefore we hypothesize that the thinning of the superior RNFL are of non-glaucomatous.

There are many in vitro studies relating to cellular toxicity caused by drugs from the opioid groups [16-19]. However, there are also conflicting studies showing neuroprotective effect on activation on opioid receptors by endogenous / exogenous opioid agonist before an ischemic insult [20,21]. Neurophysiological studies on opiate dependence shows reduction in prefrontal and temporal gray matter density [22]. Another study on heroin addicts has shown white matter impairment [8].

In our study, we noticed some limitations. The term opioid was used as it comprises of all types of opiates from substance from opium, morphine, heroin, fentanyl and methadone. We are unable to demonstrate the exact drug that causes the thinning of the retinal nerve fiber layer.

Another limitation was due to patient factor. As we know, drug abuse is a social problem and is against the law. Heroin or morphine obtained by users was by illegal means and it is unknown of the quality and purity of the drug. It is also common for unknown substance added to the drug leading to unavoidable confounding factors. Subjects are also prone for recall bias when providing history. The saving factor for our study was patients were from Methadone clinic which has good record keeping of the duration and amount of methadone taken by patient.

Conclusion

There was significant difference in the whole RNFL thickness between opioid dependent and control as examined for right eye but there was no significant difference in the left eye.

There was no significant difference in the mean central macula thickness in both opioid dependent and control group.

Superior quadrant of the optic nerve head was shown to be statistically thinner in opioid dependent group as compared to control.

This shows that there is a possible long term negative side effect of opioid usage in addition to the known negative side effects of opioids. It is recommended that further studies be conducted to monitor if the changes will lead to detectable clinical signs.

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Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics of Study

Ethical approval for the present study was obtained from the USM Human Research Ethics Committee (USM/JEPeM/272.3.(8). The study was conducted in accordance with the international Declaration of Helsinki guidelines.

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