COMPARISON OF RETINAL NERVE FIBER LAYER THICKNESS, MACULA THICKNESS AND OPTIC NERVE HEAD PARAMETERS IN OPIOID DEPENDENT AND NORMAL ADULT

BY

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Disclaimer

I hereby certify that the work in this dissertation is my own except for quotations, questionnaires and summaries which have been duly acknowledged.

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Abstrak

Pengenalan

Penyalahgunaan dadah merupakan masalah sosioekonomi yang mengancam warga awam negara kita. Jenis dadah dalam kumpulan opioid yang sering disalahgunakan di Malaysia adalah heroin dan morfin. Penyalahgunaan opioid dikaitkan dengan ketagihan dan kebergantungan sebagai kesan sampingan. Kesan sampingan yang berkaitan dengan mata adalah miosis anak mata, kemerahan konjunktiva, gangguan pergerakkan mata dan risiko komplikasi seperti endoftalmitis. Degenerasi saraf otak adalah dikaitkan dengan komplikasi penggunaan kronik dadah opioid.

Objektif

Perbandingan antara ketebalan lapisan saraf retina mata, ketebalan makula dan parameter kepala saraf optik di dalam kalangan pengguna opioid dan bukan pengguna.

Metodologi

Kajian kes kawalan antara pengguna opioid dan bukan pengguna opioid telah dilaksanakan di Klinik Methadone, Jabatan Psikiatri dan Klinik Am, Jabatan Oftalmologi Hospital Universiti Sains Malaysia. 35 pengguna opioid dan 35 bukan pengguna dikenalpastikan dan dipelawa untuk menyertai kajian ini. Pemeriksaan oftalmologi dan penyiasatan “optical coherent tomography” dengan menggunakan peralatan Heidelberg Spectralis ® OCT telah dilaksanakan.

Keputusan

Berbanding dengan bukan pengguna opioid, mata kanan kumpulan pengguna opioid didapati mempunyai purata lapisan saraf retina mata yang lebih nipis ($p<0.05$). Ketebalan lapisan saraf retina pada sukuan atasan untuk kedua-dua belah mata didapati lebih nipis dalam kumpulan pengguna opioid berbanding bukan opioid.

Kesimpulan

Penipisan awal dalam lapisan saraf retina mata mungkin merupakan tanda-tanda awal komplikasi dan kesan sampingan daripada penggunaan opioid yang kronik. Penyiasatan lanjutan adalah diperlukan untuk mengenalpasti samaada penipisan ini akan berjanjutan dalam jangka masa lama dan implikasinya kepada penglihatan pengguna opioid.

Abstract

Introduction

Drug abuse is a socioeconomic problem that affects the public of the country. 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

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. 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 both superior quadrant of the 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 with time and the implication to the patients' vision.

Chapter 1

Introduction

1.0 INTRODUCTION

1.1 Opioids

Opioid is a generic term used to describe opiates and their synthetic analogues (United Nations International Drug Control and Laboratory, 2003). Opioid substance binds to opioid receptors to create agonist, partial agonist and antagonist effects (Pathan and Williams, 2012). 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.

1.2 Epidemiology of Drug Abuse in Malaysia

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%)(*Maklumat Dadah 2014*, 2014). 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 (Vicknasingam and Navaratnam, 2008).

1.3 Effects of Opioids

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, tolerance and withdrawal symptoms when opioids are stopped abruptly (American Psychiatric *et al.*, 2013; Benyamin *et al.*, 2008; Stahl, 2000). There are many interests in the study of opioids at a molecular level. Animal studies has demonstrated neuronal cells toxicity on exposure to exogenous opioids (Atici *et al.*, 2004; Cunha-Oliveira *et al.*, 2006; Hu *et al.*, 2002; Tramullas *et al.*, 2008) with the mechanism of apoptotic cell death and oxidative stress described (Guzmán *et al.*, 2006).

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 (Firth, 2004; McLane and Carroll, 1986). 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 (Buttner *et al.*, 2000; Geibprasert *et al.*,

2010; Wang *et al.*, 2011). With the retina and optic nerve as the extension of the brain (London *et al.*, 2013), our current study is to determine if there are any changes seen in the retina nerve fiber layer due to chronic opioid usage. Presence of changes in the retinal nerve fiber may further provide data for further study on the harmful effects of opioid.

Chapter 2

Objectives

2.0 OBJECTIVES

2.1 General Objectives

To compare the means of retinal nerve fiber layer (RNFL) thickness, macula thickness and optic nerve head parameters between opioid dependent and healthy non-opioid user adults.

2.2 Specific Objectives

2.2.1 To compare the mean retinal nerve fiber layer thickness between opioid dependent and healthy non-opioid user adults.

2.2.2 To compare the mean macula thickness between opioid dependent and healthy non-opioid user adults.

2.2.3 To compare the mean optic nerve head parameters between opioid dependent and healthy non-opioid user adults.

Chapter 3

Manuscript

3.0 MANUSCRIPT

3.1 Title

Comparison Of Retinal Nerve Fiber Layer Thickness, Macula Thickness and Optic Nerve Head Parameters In Opioid Dependent And Normal Adult

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3.2 Abstract

Introduction

Drug abuse is a socioeconomic problem that affects the public of the country. 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.

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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. 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 both superior quadrant of the 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 patients' vision.

Keyword

Retinal nerve fiber layer, RNFL, Opioid, Heroin

3.3 Introduction

Opioid is a term used to describe opiates and their synthetic analogues, which includes drugs such as heroin, morphine and methadone. Based on the Malaysian National Anti-Drug Agency 2014 statistics, 64.9% of detected drug users used heroine and morphine.

In experimental laboratory studies, it was reported that street heroin induces apoptosis in rat cortical neurons (Cunha-Oliveira *et al.*, 2006) while another in vitro experiment on human fetal microglia and has demonstrated morphine-induced apoptosis (Hu *et al.*, 2002).

It is well known that heroin and morphine are associated with addiction and physical dependence. The chronic usage of these substances is known to cause neurodegeneration, cerebral atrophy and white matter impairment which has been demonstrated by neuroimaging modalities such as Computed Tomography (CT) scan and Magnetic Resonance Imaging (MRI) (Geibprasert *et al.*, 2010).

The retinal nerve fiber layer (RNFL) is an important structure in the eye as it is an extension of the ganglion cell axons, which courses along the inner portion of the retina and aggregates to form the optic nerve which continues to form the optic chiasm and optic tract (Gregory L. Skuta *et al.*, 2010). The point where the retinal axons exit the eye is described as the optic nerve head. The RNFL axons are unmyelinated within the retina and they are ideal for the visualizing and analysis of any potential neurodegeneration process (Galetta *et al.*, 2011).

Quantitative examination of the RNFL can be performed using Confocal Scanning Laser Ophthalmoscopy, Scanning Laser Polarimetry or Optical Coherent Tomography. The commonest and widely used method is by using spectral domain Optical Coherent Tomography (OCT). OCT is a non-invasive technique to obtain a

cross-sectional image of the retinal. Current spectral domain OCT has an advantage of better quality and resolution, improved reproducibility of images and measurement as compared to the previous generation of time domain OCT (Kiernan *et al.*, 2010). To our knowledge, there are no previous studies that investigate the RNFL thickness in opioid dependent users using OCT.

The aim of this study is to investigate if there are structural changes in the retinal nerve fiber layers and macular in opioid dependent and normal adults. We hypothesize that with chronic usage of opioids, there will be early thinning of the retinal nerve fiber layer as compared to those who are not users.

3.4 Methodology

3.4.1 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.

3.4.2 Ophthalmological Assessment

Ophthalmological assessment included measurement of uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) using Snellen Visual Acuity Chart. BCVA 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.

3.4.3 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.

3.4.4 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 controlling for age. Statistical significance was reported at $p<0.05$.

3.4.5 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 (Leung *et al.*, 2010) 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 $p<0.05$

3.5 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.

Data from both eyes were collected. Analysis by paired t-test was performed to compare differences between right and left eye in each group.

For the opioid dependent group, RNFL parameters shows no differences between eye except in the Temporal group, OD 75.6 ±12.7 vs OS 70.2 ± 11.1, mean of difference 5.4 ($p=0.001$, 95% CI 2.4,8.4).

For the healthy control group, there was inter eye variability seen in Superior quadrant, OD 133.1 ± 13.9 vs OS 139.5 ± 14.2, mean of difference -6.3 ($p<0.001$, 95% CI -9.5,-

3.1) and Nasal quadrant, OD 76.9 ± 14.5 vs OS 71.3 ± 11.5, mean of difference 5.6 (p=0.015, 95% CI 1.1,10.0).

For both opioid dependent and healthy control, there was no inter eye variability in intraocular pressure and vertical cup-to-disc ratio.

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 data for both groups

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

[a]Statistical test : t Test

Table 2: Retinal Nerve Fiber Layer Thickness Between Opioid Dependent and Control in Right Eye

RNFL thickness (microns)	n	Adj. Mean (95% CI)[a]	Adj. Mean diff. (95% CI)[b]	F-stat (df)	P value
OD Whole Retina					
Opioid	35	97.37 (93.59, 101.16)	7.26 (1.40, 13.09)	6.19 (1,70)	0.015
Control	35	104.63 (100.85, 108.42)			
OD Macula Thickness					
Opioid	35	263.21 (256.05, 270.38)	9.2 (-1.83, 20.23)	2.77 (1,70)	0.101
Control	35	272.42 (265.25, 279.58)			
OD Superior					
Opioid	35	118.42 (112.97, 123.87)	14.36 (5.97, 22.75)	11.68 (1,70)	0.001
Control	35	132.78 (127.33, 138.23)			
OD Inferior					
Opioid	35	126.27 (119.78, 132.76)	8.89 (-1.10, 18.87)	3.15 (1,70)	0.080
Control	35	135.16 (128.67, 141.65)			
OD Temporal					
Opioid	35	75.27 (71.01, 79.52)	-1.99 (-8.54, 4.57)	0.37 (1,70)	0.550
Control	35	73.28 (69.02, 77.54)			
OD Nasal					
Opioid	35	69.61 (63.76, 75.47)	7.8 (-1.21, 16.81)	2.99 (1,70)	0.089
Control	35	77.42 (71.56, 83.27)			

[a]Adjusted mean using ANCOVA after controlling for age
[b]Least square difference for 95% CI for difference

Table 3: Retinal Nerve Fiber Layer Thickness Between Opioid Dependent and Control in Left Eye

RNFL thickness (microns)	n	Adj. Mean (95% CI)[a]	Adj. Mean diff. (95% CI)[b]	F-stat (df)	P value
OS Whole Retina					
Opioid	35	99.96 (96.09, 103.83)	3.5 (-2.45, 9.46)	1.38 (1,70)	0.244
Control	35	103.47 (99.60, 107.34)			
OS Macula Thickness					
Opioid	35	263.31 (256.42, 270.20)	9.77 (-0.83, 20.38)	3.38 (1,70)	0.070
Control	35	273.09 (266.20, 279.98)			
OS Superior					
Opioid	35	123.02 (117.96, 128.07)	15.37 (7.59, 23.15)	15.53 (1,70)	<0.001
Control	35	138.38 (133.33, 143.44)			
OS Inferior					
Opioid	35	129.40 (122.61, 136.18)	3.24 (-7.20, 13.68)	0.38 (1,70)	0.538
Control	35	132.63 (125.85, 139.42)			
OS Temporal					
Opioid	35	70.33 (66.40, 74.25)	1.95 (-4.10, 7.99)	0.41 (1,70)	0.522
Control	35	72.27 (68.35, 76.20)			
OS Nasal					
Opioid	35	76.67 (70.59, 82.75)	-6.25 (-15.61, 3.10)	1.78 (1,70)	0.187
Control	35	70.42 (64.34, 76.49)			

[a]Adjusted mean using ANCOVA after controlling for age
[b]Least square difference for 95% CI for difference

3.6 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 (*Maklumat Dadah 2014*, 2014). 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. In our study, intereye asymmetry was only found in temporal quadrant of opioid dependent and superior and nasal in control group. Intereye RNFL asymmetry in normal subjects has been found in other studies which mentioned that mean RNFL thickness should not differ more than 9-12μm (Budenz, 2008).

Many researches have been done in regards to RNFL thickness and its relation to diseases such as Alzheimer's disease, multiple sclerosis and schizophrenia, which showed early abnormal changes (Chu *et al.*, 2012; Frohman *et al.*, 2008; London *et al.*, 2013; Paquet *et al.*, 2007). In our literature search, we could not find any studies that investigated RNFL thickness in subjects taking illicit drugs from opioids group.

Our study found that 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. However, asymmetrical changes can actually occur as demonstrated in open angle glaucoma as OCT studies has been performed in order to detect early primary open-angle glaucoma (Field *et al.*, 2016; Sullivan-Mee *et al.*, 2013). In regards to the comparison of macular

thickness in both groups, there were no statistical differences seen. As the retina 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 (Gupta *et al.*, 2016; Jonas *et al.*, 1991). 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. IOP for the opioid dependent group was found to be lower as compared to the healthy control group (13.7 ± 2.4 vs 14.74 ± 2.3). This finding was similar to findings by previous study (Drago *et al.*, 1985). Similarly, few experimental animal studies have shown opioid derivatives induced reduction in IOP (Dortch-carnes and Russell, 2006; Russell *et al.*, 2000). There was no statistical difference in cup-disc-ratio between the two groups and there were no intereye asymmetry of cup-disc-ration and IOP to suggest glaucomatous changes.

There are many in vitro studies relating to cellular toxicity caused by drugs from the opioid groups. The exact mechanism of cell death was not known but the studies have shown neuronal cells death caused by cell apoptosis and necrosis (Berrios *et al.*, 2008; Cunha-Oliveira *et al.*, 2006; Hu *et al.*, 2002; Mao *et al.*, 2002; Tramullas *et al.*, 2007; Tramullas *et al.*, 2008). In the brain, white matter and gray matter was shown to be

impaired in opioid dependent (Buttner *et al.*, 2000; Lin *et al.*, 2012; Lyoo *et al.*, 2006; Wang *et al.*, 2011).

However, there are also contrasting experimental studies showing neuroprotective effect of opioids in the retina. In an experimental study of induced ischemic retinopathy and subsequent reperfusion, morphine administration post reperfusion has shown a protective effect against ischemia-reperfusion injury (Riazi-Esfahani *et al.*, 2009). Activation of opioid receptors in the eye has been linked to be neuroprotective against glaucomatous injury by mechanism of suppression of TNF-α production (Husain, 2015; Husain *et al.*, 2012a; Husain *et al.*, 2012b; Husain *et al.*, 2009)

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.

3.7 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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