EVALUATION OF RETINAL NERVE FIBER LAYER THICKNESS, MACULAR THICKNESS AND CHOROIDAL THICKNESS IN ERECTILE DYSFUNCTION PATIENTS ON SILDENAFIL

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ABSTRAK

Pengenalan

Sildenafil sitrat ialah perencat selektif yang kuat terhadap enzim *cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5)* yang membantu proses ketegangan zakar. Di peringkat mata, kesannya sepuluh kali ganda lebih lemah terhadap enzim PDE6 yang banyak terdapat di retina. Walaupun profil keselamatannya telah disahkan, banyak kajian menyabitkan sildenafil dengan kecederaan toksik mata. Dapatan kajian berkenaan ketebalan lapisan serat mata (RNFL), makula dan koroid juga bercanggah. Jadi pengguna sildenafil masih berisiko mendapat komplikasi kebutaan sepanjang tempoh penggunaannya. Walau kesan toksik akut melibatkan dos dapat dikenalpasti, implikasi jangka panjang berkait penggunaan sildenafil dan jumlah dos kumulatif masih tidak mempunyai dapatan yang jelas. Kajian ini menilai hubungan antara tempoh penggunaan sildenafil terhadap RNFL, makula dan koroid.

Kaedah kajian

Kajian rentas ini telah dijalankan terhadap 47 pesakit disfungsi ereksi (ED) yang menggunakan sildenafil di Hospital Universiti Sains Malaysia daripada Julai 2020 hingga Jun 2021. Subjek memenuhi syarat kajian dan mempunyai pemeriksaan mata normal akan menjalani *optical coherent tomography* (OCT) untuk mengukur ketebalan RNFL, makula dan koroid. Analisa statistik regresi linear dijalankan untuk menilai hubungan antara tempoh penggunaan dengan parameter-parameter OCT. Faktor lain yang berkaitan turun dinilai.

Keputusan

Empat puluh tujuh pesakit ED dengan umur purata 54.30±8.41 tahun direkrut (julat 41 - 70). Tiada pesakit yang mengadu masalah ganguan visual disetiap penggunaan sildenafil. Majoriti mempunyai skor kekerasan ketegangan 2 (EHS2) (zakar mengeras namun tidak cukup untuk penetrasi) (93.6%). Terdapat kolerasi yang signifikan antara diabetes mellitus (DM) (r=0.330, P=0.023), EHS (r=-0.469, P=0.001) dan jumlan dos kumulatif (r=0.806, P=<0.001) dengan tempoh penggunaan. Tempoh penggunaan mempunyai hubungan linear yang signifikan dengan purata RNFL (b = -0.284, P=<0.001), RNFL atas (b = -0.195, P=0.018), and RNFL bawah (b = -0.887, P=<0.001), mendedahkan terdapat penipisan RNFL dengan setiap peningkatan tempoh penggunaan. Regresi linear berbilang menunjukkan purata RNFL juga dipengaruhi oleh jumlah dos kumulatif (b = -0.003, P = 0.029). Tiada hubungan yang signifikan antara tempoh penggunaan dan pemboleh ubah lain didapati pada ketebalan makula. Terdapat hubungan linear signifikan antara tempoh penggunaan dengan ketebalan koroid sub-foveal (b = 0.640, P<0.001).

Kesimpulan

Sildenafil secara amnya tidak menyebabkan simptom visual ketara, namun perubahan mata subklinikal; ketebalan RNFL dan koroid tetap dipengaruhi oleh tempoh penggunaan. Pemantauan jangka panjang dikalangan pesakit yang bergantung kepada sildenafil adalah disyorkan.

ABSTRACT

Introduction

Sildenafil citrate is a potent selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) enzymes, which enhances nitric oxide (NO)-mediated erection. At the ocular level, it has a tenfold less potent inhibitory activity against the cGMP dependent PDE6 enzyme which is abundant in the retina. Despite the established safety profile, multiple reports had been published associating sildenafil to ocular injury. Some studies about the retinal nerve fiber layer (RNFL), macula and choroids are also conflicting. Still, sildenafil-dependent-men may be at risk of getting blinding ocular events throughout their duration of use. Although acute dose related toxicity effect has been established, implication of long-term regular use of sildenafil and total cumulative sildenafil dose effects are still somewhat unclear. We evaluate the relationship between duration of sildenafil use to the RNFL, macular and choroidal thickness.

Methods

A hospital based cross-sectional study was done among 47 erectile dysfunction (ED) patients on sildenafil in Hospital Universiti Sains Malaysia between July 2020 and June 2021. The subjects fulfilled the inclusion criteria with normal ocular examinations underwent optical coherent tomography (OCT) examination to evaluate RNFL, macular and choroidal thickness. Linear regression analysis was done to evaluate the relationship between duration of use with the OCT parameters. Other possible associated factors were also evaluated.

Results

Forty-seven ED patients with the mean age of 54.30±8.41 years old recruited (ranging 41 to 71). The patients did not complain any visual disturbance on each sildenafil use. Majority had erectile hardness score (EHS) of 2 (penis is hard but not hard enough for penetration) (93.6%). There was significant correlation between diabetes mellitus (DM) (r=0.330, P=0.023), EHS (r=-0.469, P=0.001) and total cumulative dose (r=0.806, P=<0.001) with the duration of use. Duration of use had significant linear relationship with the average RFNL (b = -0.284, P=<0.001), superior RNFL (b = -0.195, P=0.018), and inferior RNFL (b = -0.887, P=<0.001) revealing reduced RNFL thickness with increased duration of use. Multiple linear regression (MLR) reveals average RNFL was also influenced by total cumulative dose (b = -0.003, P = 0.029). No significant relationship between duration of use and other variables are observed to the macular thickness. Significant linear relationship was observed between duration of use with sub-foveal choroidal thickness (b = 0.640, P<0.001).

Conclusions

Sildenafil in general does not cause visual symptoms, however subclinical ocular changes; RNFL thinning and choroidal thickening may be influenced by its duration of use. Long term ocular monitoring of sildenafil-dependent ED patients is recommended.

CHAPTER 1:

INTRODUCTION

1.1 ERECTILE DYSFUNCTION

Erectile dysfunction (ED) is defined as the inability to attain and/or maintain penile erection sufficient for satisfactory sexual intercourse (NIH Consensus Conference, 1993). The worldwide prevalence of ED is 7–52% (Korenman, 2004) and comparison with other studies showed marked ethnic variation in the prevalence of ED internationally. The prevalence of ED (mild to severe) in Malaysia was reported to be 76.1% among patients more than 50 years of age (Khoo et al., 2008). Approximately more than 90% of men aged over 40 years with ED have an organic cause, with the most common aetiology of vascular diseases (Kendirci and Hellstrom, 2007). Findings from several cross-sectional and longitudinal studies have linked the development of erectile dysfunction to diabetes mellitus, hypertension, hyperlipidaemia, metabolic syndrome, depression, and lower urinary tract symptoms (Raymond C. Rosen et al., 2009).

1.1.1 Pathogenesis of erectile dysfunction

Penile erection is a complex physiological process that is mediated by psychological, neuronal, and vascular events. Arterial inflow to the corpus cavernosa is increased secondary to smooth muscle relaxation in the afferent arterioles (Vardi and Siroky, 1990). The most important mediator of corpus cavernosum smooth muscle relaxation, and subsequent erection is nitric oxide (NO) (N. Kim et al., 1991; Rajfer et al., 1992). Following the stimulation by acetylcholine (ACh), NO is synthesised and released directly from parasympathetic non-adrenergic, non-cholinergic nerves and from vascular endothelial cells (Palmer et al., 1988).

Normal sexual function is a biopsychosocial process that involves the coordination of psychological, endocrine, vascular, and neurological systems (Prieto, 2008). Any disturbances in this erectile pathway coordination will lead to ED. It can be classified as psychogenic, organic, or mixed psychogenic-organic. Psychogenic ED can be due to past traumatic experiences, mental health problems, acute family relationships, and major life events. Performance anxiety which described as fear of failure during intercourse was identified to be the most important cause of ED. Meanwhile, organic causes can be due to neurogenic, vasculogenic, endocrinological, and local (penile) factors. Neurogenic ED mainly is due to failure in neurological transmission in normal erectile function. Endocrinological cause usually is attributed to testosterone deficiency which plays very important role in sexual desire. Vasculogenic factors mainly cause penile arterial insufficiency which lead to failed erection (Dougherty, 2018).

1.1.2 Diagnosis of erectile dysfunction

Assessment of ED is done to establish diagnosis, to identify the cause of the disorder, and to ascertain risk factors and potentially life-threatening comorbid disorders associated with ED (Dougherty, 2018). Although laboratory-based diagnostic procedures are available, it has been proposed that sexual function is best assessed in a naturalistic setting with patient self-report techniques (Raymond C. Rosen et al., 1997). An objective abridged five-item version of the 15-item International Index of Erectile Function was developed (IIEF-5) to diagnose the presence and severity of ED. The IIEF-5 focuses on erectile function and intercourse satisfaction and possess favourable properties for detecting the presence and severity of ED (R. C. Rosen et al., 1999). Subjective measurement of erection is assessed by Erection Hardness Score (EHS), a single-item patient-reported outcome for scoring the hardness of erection. It is usually used in

clinical setting due to its easy to use and highly responsive to treatment (Cappelleri and Hvidsten, 2007).

1.1.3 Treatment of erectile dysfunction

Sildenafil citrate is a potent selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) enzymes, which present in vasculature smooth muscle (Beavo, 1995; Moreland et al., 1998). Sildenafil citrate enhances the NO-cGMP pathway, which mediates smooth muscle relaxation of the corpora cavernosa and penile arteriolar smooth muscles and causes a significant improvement in penile blood flow and erectile function (Ballard et al., 1998). This action, in turn, improves the rate of successful sexual intercourse in men with ED (Goldstein et al., 1998).

Sildenafil citrate was first approved by the Food and Drug Administration (FDA) for use in men with ED on March 27, 1998. The recommended dose of sildenafil citrate is 50 mg once per day, approximately 60 minutes before sexual activity with lasting effects up to four hours. Based on efficacy and tolerability, the minimum and maximum recommended doses are 25 and 100 mg respectively (Azzouni and Abu samra, 2011). It is rapidly absorbed, exhibiting an oral bioavailability of 40%–41%, and reaches maximal levels within 0.5–2 hours after oral ingestion. The plasma clearance of sildenafil citrate is around 10 mL/min/kg. It is predominately metabolized by the liver (cytochrome P4503A4 isoenzyme), and its mean terminal half-life is 3–5 hours (M. Moschos and Nitoda, 2016).

Sildenafil citrate ranked at 45 of all U.S. Pharmaceuticals. Increasing trends of use observed worldwide with the average sale of 1.8 million units every year since 2011 until 2014

(Drug.com, n.d.). Malaysia recorded as the world's biggest consumer of Viagra within two years introduced in the market with reported 40,000 Malaysian had been taking it regularly (BBC News, n.d.).

1.2 SILDENAFIL AND OCULAR EFFECTS

Sildenafil citrate has weak inhibitory activity against the cGMP dependent PDE6 enzyme, which is tenfold less potent than on PDE5 (Wallis et al., 1998). PDE6 is a unique isoenzyme located in the retina, where the rod and cone outer segments are in high concentration (Lagnado, 2000). The weak PDE6 inhibitory action causes some patients on sildenafil citrate to complain blurry vision, transient colour tinge, increased sensitivity to light as well as transient impairment of colour discrimination (A M Laties and Fraunfelder, 1999; Morales et al., 1998).

The most common adverse events reported by patients using sildenafil citrate have been predominantly transient and mild to moderate in severity, and have included headache, facial flushing, rhinitis, and dyspepsia. These effects likely result from sildenafil citrate inhibition of PDE5 in the smooth muscle of the systemic vasculature and the digestive tract and sildenafil citrate inhibition of cGMP-specific PDE6 in the retina (Stockman et al., 2007). Known ocular adverse effects include blue tinge to the environment and changes in brightness perception, usually in the form of increased sensitivity to light. These symptoms are mild and reversible. Serious ocular complications reported in association with sildenafil citrate include non-arteritic anterior ischemic optic neuropathy (NAION), cilio-retinal artery occlusion, central retinal vein occlusion (CRVO), and pupil sparing third nerve palsy (Azzouni and Abu samra, 2011).

The time to onset and duration of recognised visual symptoms as described, were consistent with the pharmacokinetic profile of sildenafil citrate. Symptoms occurred during the usual time

of peak plasma free sildenafil citrate concentrations and stopped at times, consistent with its metabolism and elimination (Milligan et al., 2002). Almost all visual adverse events occurred within two hours of sildenafil citrate dosing. The duration of the visual symptoms was less than four hours, and nearly all patients who reported visual disturbances reported that they did not adversely affect day-to-day life (Alan M. Laties and Zrenner, 2002).

1.3 SILDENAFIL EFFECT ON RETINAL NERVE FIBER LAYER (RNFL)

Sildenafil citrate has a potent inhibitory effect of cGMP-PDE5 enzymes and can cause systemic hypotension. It is postulated that NO activation may reduce optic nerve perfusion and disrupt its autoregulation (Kerr and Danesh-Meyer, 2009). Although there was no unfavourable effect of single dose of sildenafil citrate treatment in acute phase on the retinal nerve fiber later (RNFL) (Örnek et al., 2015), multiple cases have been reported involving optic neuropathy and nerve fiber layer injuries post sildenafil citrate ingestion.

This is parallel to Bordas et al reported a case of NAION with pseudo thickening of nerve fiber layer (Bordas et al., 2018). Moschos and Margetis noted the simultaneous presentation of NAION in a 55-year-old man, who had received 50 mg of sildenafil citrate four to five times a month, over the previous eight months. The examination at presentation revealed a right optic disk edema, a left crowded optic disk, and an inferior altitudinal defect in the visual fields of both the eyes. Three weeks after the discontinuation of the drug, both visual acuity and optic disc features were restored, but the visual field defect of the right eye remained unchanged, lasting even three months later (M. M. Moschos and Margetis, 2011). Another case of unilateral NAION was reported in a 51-year-old man with a history of sildenafil citrate use for the last six months at least once a week. One year after receiving three steroid injections and the

discontinuation of sildenafil citrate, visual field defects were persistent, although visual acuity was improved (Felekis et al., 2011). In a review of 67 double-blind placebo-controlled trials and the post-marketing safety database, sildenafil citrate, in general, was well tolerated at a dose of 50 or 100 mg in men with ED. The analysis, however, could not reveal any causal link between sildenafil citrate and ocular complication such as NAION (Giuliano et al., 2009).

A recent animal study was done to evaluate the histological effect of sildenafil citrate for eight weeks and more in adult male rats. It was found that the retina and optic nerve had vacuolations, thickened basal lamina, with congested blood capillaries and apoptotic endothelial and pericytic cells. Glial cells revealed morphological changes; Müller cells lost their processes, activated microglia, astrocytic clasmatodendrosis, degenerated oligodendrocytes surrounded by disintegrated myelin sheaths of the optic nerve fibers. With multiple reported cases of sildenafil citrate related optic nerve and retinal injuries at present, the implications of the long-term daily use of sildenafil citrate on the retina and optic nerve are somewhat still unclear (Eltony and Abdelhameed, 2017).

1.4 SILDENAFIL EFFECT ON MACULA AND CHOROIDAL LAYERS

Sildenafil citrate has weak inhibitory activity against the cGMP dependent PDE6 enzyme, which is tenfold less potent than on PDE5 (Izadi et al., 2012). PDE6 is a unique isoenzyme in its restricted localization to the retina and plays a role in the conversion of light stimulation to an electrical signal (Lagnado, 2000). Sildenafil citrate also has a high affinity to melanin, which causes its prolonged accumulation in the retina (Ballard et al., 1998; Omori and Kotera, 2007). These effects potentiate the possibility of ocular toxicity.

Yanoga et al. reported a case of persistent retinal toxicity after ingesting a bottle of liquid sildenafil citrate without using 50 mg/ml measuring pipette given. Optical coherence tomography (OCT) B-scans demonstrated diffuse nodular thickening and irregularities of the central ellipsoid zone associated with thinning and poor delineation of the interdigitation zone (Yanoga et al., 2018). Additionally, Li et al. reported a case of high dose sildenafil citrate ingestion with outer retina damage in the foveal area, following consumption of 2000 mg sildenafil citrate. OCT finding revealed abnormal hypo reflectivity of the ellipsoid zone, the outer segments of photoreceptors, and the interdigitation zone in the binocular foveal area (Li et al., 2018).

A case of persistent ocular toxicity also reported in a patient taking seven times more than the recommended dose of sildenafil citrate. The patient had blurry vision post-ingestion, and the OCT scan revealed increased reflectivity at the inner/outer segment junction line as well as showed flattening of the inner/outer segment junction line peak in both eyes. Central scotoma and enlarged blind spots demonstrated in the automated visual field (H. D. Kim et al., 2017). S. Vance et al found an increased choroidal thickness from Enhanced Depth Imaging Optical Coherence Tomography (EDI-OCT) at 1 hour and 3 hours after the ingestion of 100 mg of sildenafil citrate, which appears to tally with other studies suggesting association of PDE5 inhibitor with central serous retinopathy (Vance et al., 2011).

Quiram et al. reported two cases of Viagra-associated serous macular detachment in patients on sildenafil citrate for one- and two-years duration. It was postulated that the potent vasodilator effect of sildenafil citrate could cause idiosyncratic engorgement of the choroidal vasculature. This leads to leakage across the RPE and accumulation of subretinal fluid (Quiram et al., 2005). Histological findings support available in rats, which showed dilated choroidal capillaries after

four weeks of sildenafil citrate (Vatansever et al., 2003). Kumari et al. also reported four cases of paramacular oedema and 11 cases of retinal ischemic features among 100 patients who were on 6-month use of sildenafil citrate (Kumari et al., 2016).

As sildenafil citrate is a treatment and not a cure, many men may choose to use it for an extended period (McMurray et al., 2007), however, the implications of the long-term daily use of it on the retina and optic nerve are unclear (Gabrieli et al., 2001; Sponsel et al., 2000). To date, available data indicate that there is no evidence showing repeated intermittent use of sildenafil citrate produces any structural damage or clinically significant functional changes to the retina sildenafil citrate (A. Laties and Sharlip, 2006). However, multiple cases involving optic nerve and retinal damage have been reported in patients on prolonged use of sildenafil citrate.

1.5 RATIONALE OF STUDY

Sildenafil citrate is a potent cGMP-PDE5 enzymes inhibitor which causes NO activation and significant improvement in penile blood flow and erectile function. It is a form of treatment and requires prolonged duration of use. Sildenafil citrate has known mild adverse effects to the eye including blue tinge to the environment and changes in brightness perception, usually in the form of increased sensitivity to light. However multiple case reports and animal studies have found the effect of sildenafil citrate to the optic nerve and retina which may be blinding to the eye.

As the use of sildenafil citrate is increasing with the prevalence of erectile dysfunction in Malaysia, it is important to detect early possible ocular effects due to its use. Previous studies done were mostly to study the acute effects of sildenafil citrate. It was proven significantly that acute ocular findings are in relation to peak plasma free concentrations which also resolved after the drug has been metabolised and eliminated. Although post-marketing reports and controlled trials couldn't find the causal link between sildenafil citrate and serious ocular complications, multiple cases of optic nerve and retinal injury associated with the use of sildenafil citrate have been reported till date. Study results of ocular sildenafil citrate effects on the RNFL, macula and choroid are also conflicting and some inconclusive.

Sildenafil citrate tends to accumulate longer in the retina due to its high affinity towards melanin. This can lead to local toxic effect to the retinal layer (Ballard et al., 1998; Omori and Kotera, 2007). The inhibition of PDE5 causes increases systemic NO and cGMP. Chronic cGMP accumulation is also believed to cause retinal toxicity (H. D. Kim et al., 2017). Additionally, NO activation may reduce optic nerve perfusion and disrupt its autoregulation. It

also causes disruption in blood ocular barrier, limiting retinal perfusion (Danesh-Meyer and Levin, 2007). This continuous hypotensive insult could possibly cause injury to the optic nerve and retina in a long run.

This study is done to fill the gap of knowledge in evaluating RNFL thickness, macular thickness and choroidal thickness in ED patients on sildenafil citrate use. OCT is a high-resolution cross-section imaging that is used to measure the structural thickness of RNFL, macular and choroidal layers. This is a very useful tool to detect early anatomical changes as well as to evaluate retinal toxicity and easily available in the eye clinic. They are crucial to monitor the progression and evaluate signs of optic nerve and retinal toxicity in patients on sildenafil citrate which could not be detected on routine eye examination. Early detection is important to prevent a permanent visual loss related to optic nerve and retinal toxicity. It also can be used in future to empower the guideline on eye assessment in Malaysia for ED patients on sildenafil citrate .

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CHAPTER 2:

STUDY OBJECTIVES

2.1 GENERAL OBJECTIVE

To evaluate the retinal nerve fiber layer (RNFL) thickness, macular thickness, and choroidal thickness in erectile dysfunction (ED) patients on Sildenafil.

2.2 SPECIFIC OBJECTIVES

2.2.1. To determine the relationship between the duration of use and RNFL thickness in ED patients on Sildenafil.

2.2.2. To determine the relationship between the duration of use and macular thickness in ED patients on Sildenafil.

2.2.3. To determine the relationship between the duration of use and choroidal thickness in ED patients on Sildenafil.

CHAPTER 3:

MANUSCRIPT

EVALUATION OF RETINAL NERVE FIBER LAYER THICKNESS, MACULAR THICKNESS AND CHOROIDAL THICKNESS IN ERECTILE DYSFUNCTION PATIENTS ON SILDENAFIL

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ABSTRACT

Introduction: Sildenafil citrate is a treatment for erectile dysfunction (ED). Despite the established safety profile, multiple reports have associated sildenafil to ocular injury. We evaluate the relationship between duration of use with the retinal nerve fiber layer (RNFL), macular and choroidal thickness. **Methods:** A cross-sectional study was done between July 2020 and June 2021, among 47 ED patients on sildenafil. The subjects fulfilling the inclusion criteria underwent optical coherent tomography (OCT) to evaluate RNFL, macular and choroidal thickness. Linear regression analysis was done to evaluate the relationship between duration of use with the OCT parameters. Other possible associated factors were evaluated. **Results:** Forty-seven patients with the mean age of 54.30±8.41 years old recruited. These patients had not experienced visual disturbance on each sildenafil use. There were significant correlations between diabetes mellitus (DM) (r=0.330, P=0.023), erection hardness score (EHS) (r=-0.469, P=0.001) and total cumulative dose (r=0.806, P=<0.001) with duration of use. Duration of use had significant negative linear relationship with the average RFNL (b = -0.284, P=<0.001), superior RNFL (b = -0.195, P=0.018), and inferior RNFL (b = -0.887, P=<0.001). Multiple linear regression (MLR) reveals average RNFL was also influenced by total cumulative dose (b = -0.003, P = 0.029). No significant relationship observed to the macular thickness. Significant linear relationship observed between duration of use with sub-foveal choroidal thickness (b = 0.640, P<0.001). **Conclusion:** Sildenafil in general does not cause visual symptoms, however subclinical ocular changes; RNFL thinning and choroidal thickening may be influenced by its duration of use. Long term ocular monitoring of sildenafil-dependent ED patients is recommended.

Keywords: Sildenafil Citrate, Erectile Dysfunction, Tomography, Optical Coherence