THE EFFICACY OF INTRAVITREAL TRIAMCINOLONE VERSUS LASER PHOTOCOAGULATION IN THE PRIMARY TREATMENT OF DIABETIC MACULAR OEDEMA

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DISCLAIMER

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

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CONTENTS Page

LIST OF TABLES

LIST OF FIGURES

ABSTRAK

Objektif : Untuk membandingkan efikasi dan keselamatan suntikan ubat 'triamcinolone' ke dalam vitrus berbanding rawatan 'laser' terapi dalam rawatan awal penyakit bengkak makula pada individu yang menghidap DM.

Tatacara: Seramai 40 orang pesakit DM yang baru didiagnosa dengan bengkak macula telah menyertai kajian ini. Pesakit dibahagikan secara rambang kepada dua kumpulan iaitu 20 orang pesakit bagi setiap kumpulan di mana satu kumpulan menjalani rawatan 'laser' dan satu kumpulan lagi menjalani rawatan suntikan ubat 'triamcinolone' ke dalam vitrus. Sebanyak 4mg ubat 'triamcinolone' 0.1ml padu digunakan dan rawatan 'laser' dibuat berdasarkan garis panduan ETDRS. Semua pesakit menjalani pemeriksaan indeks kebengkakan makula menggunakan mesin HRT II dan pemeriksaan ketajaman penglihatan mata dengan carta Snellen pada peringkat permulaan dan pada tiga bulan selepas rawatan. Peningkatan tekanan dalam mata, kekeruhan pada kanta mata dan jangkitan kuman pada bola mata adalah antara perkara yang diperhatikan bagi menilai tahap keselamatan suntikan 'triamcinolone' ke dalam vitrus.

Keputusan: Purata ketajaman penglihatan bagi kumpulan suntikan triamcinolone adalah 0.935(0.223) pada peringkat awal dan 0.405(0.223) pada tiga bulan, $p<0.01$. Purata ketajaman penglihatan bagi kumpulan laser adalah 0.795(0.315) pada peringkat awal dan

0.525(0.289) pada tiga bulan, $p<0.01$. Kedua-dua bentuk rawatan tidak menunjukkan perbezaan yang signifikan selepas tiga bulan pada ketajaman penglihatan, $p=0.151$. Purata indeks kebengkakan makula bagi kumpulan suntikan triamcinolone adalah 2.539 (0.914) pada peringkat awal dan 1.753 (0.577) pada tiga bulan, $p<0.01$. Purata indeks kebengkakan makula bagi kumpulan laser adalah 2.139 (0.577) pada peringkat awal dan 1.711(0.472) pada tiga bulan, $p<0.01$. Kedua-dua bentuk rawatan tidak menunjukkan perbezaan yang signifikan selepas tiga bulan pada indeks kebengkakan makula, $p=0.811$. Purata tekanan dalam mata sebelum dan selepas rawatan menunjukkan peningkatan yang signifikan pada pesakit yang mendapat suntikan triamcinolone, $p=0.032$. Tidak terdapat perubahan yang ketara pada kekeruhan kanta mata selepas tiga bulan pada kedua-dua kumpulan rawatan, $p=0.688$. Tiada insiden jangkitan dalam mata selepas tiga bulan pada pesakit yang mendapat rawatan suntikan triamcinolone.

Kesimpulan : Kedua-dua bentuk rawatan, suntikan triamcinolone dan laser sebagai rawatan awal berkesan dalam merawat penyakit bengkak makula disebabkan DM. Suntikan triamcinolone adalah prosedur yang selamat.

ABSTRACT

Objective: To compare the efficacy and safety of intravitreal triamcinolone injection to laser photocoagulation in the primary treatment of diabetic macular oedema.

Methodology: Forty patients with newly diagnosed diabetic macular oedema were randomized into 2 groups 20 in 4mg intravitreal triamcinolone acetonide (IVTA) injection of and 20 in laser photocoagulation group. Evaluation was done at three months and the macular oedema was quantified using HRT II. Intraocular pressure elevation, lenticular opacity and endophthalmitis were observed.

Results: Mean visual acuity for IVTA group was 0.935(0.223) at baseline and 0.405(0.223) at three months, $p<0.01$. Mean visual acuity for laser group was 0.795(0.315) at baseline and 0.525(0.289) at three months, $p<0.01$. However, there was no statistically significant difference between the two groups, $p=0.151$. Mean macular oedema index for IVTA group was 2.539 (0.914) at baseline and 1.753 (0.577) at three months, $p<0.01$. Mean macular oedema index for laser group was 2.139 (0.577) at baseline and 1.711(0.472) at three months, $p<0.01$. However, there was no statistically significant difference between the two groups ($p=0.811$). The mean intraocular pressure was statistically significant pre and post IVTA injection ($p=0.032$). There was no significant

cataract progression at three months in both groups, p=0.688 and no incidence of endophthalmitis post IVTA injection at three months review.

Conclusion: Both IVTA and laser photocoagulation demonstrate good outcome as primary treatment in diabetic macular oedema patients. The IVTA is a relatively safe procedure.

1.0 INTRODUCTION

1.1 STUDY INTRODUCTION

Diabetic retinopathy and diabetic macular oedema (DME) are the leading causes of blindness in an increasing number of patients with diabetes. Reduction of visual acuity in DME results from accumulation of fluid produced from a rupture of the blood-retinal barrier into the inner nuclear layer of the retina. DME is diagnosed clinically on biomicroscopy examination. The thickened macula can be visualized on slit lamp examination using 90D / 78D lens. The retinal thickness can be measured / quantified by OCT (optical coherent tomography), Confocal laser scanning (HRT II – Heidelberg Retinal Tomography II) or Retinal Thickness Analyzer.

The standard treatment of DME is laser photocoagulation which reduces the risk of visual loss in 60% of patients. However recurrences are common and despite laser treatment, 26% of patients with DME experienced progressive loss of vision (Sutter *et al.*, 2004). Furthermore, 40% of treated eyes that had retinal oedema involving the centre of the macula at baseline still had oedema involving the centre at 12 months, as did 25% of treated eyes at 36 months (Ip, 2004). The frequency of an unsatisfactory outcome following laser photocoagulation in some eyes with DME has prompted interest in other treatment modalities.

Other treatment modalities such as pharmacologic therapy with oral protein kinase C inhibitors and antibodies targeted at vascular endothelial growth factor (VEGF) are still under investigation.

Triamcinolone Acetonide has been shown experimentally to reduce the breakdown of blood retinal barrier (Wilson *et al.*, 1992). It down regulates the production of vascular endothelial growth factor; a known vascular permeability factor hence reduced the vascular permeability. Stabilization of the blood retinal barrier introduces a rationale for Triamcinolone Acetonide treatment in diabetic macular oedema. Intravitreal injection has been proposed as a way to efficiently deliver the drug to the posterior portion of the eye, in close proximity to the retina.

Intravitreal Triamcinolone Acetonide (IVTA) has proved to be effective in the treatment of diabetic macular oedema from previous study. It constitutes a newer, less destructive treatment modality in the management of diabetic macular oedema. Two previous studies of primary intravitreal Triamcinolone in DME (Ozkiris et al., 2004, Karacorlu et al., 2005) have shown improvement on visual acuity as well as central macular thickness.

A study by Bakri and Beer in 2004 on intravitreal Triamcinolone injection on DME patients, also showed promising therapeutic method in those eyes (Bakri and Beer, 2004). Massin *et. al.*(2004) compared the use of intravitreal Triamcinolone as an adjunctive

therapy in DME eyes which failed laser treatment where it effectively reduced the macular thickening (Massin *et al.*, 2004). Jonas JB et. al. in 2003 reported in their prospective, interventional, clinical case series study, the visual acuity had significantly improved with intravitreal Triamcinolone injection (Jonas *et al.*, 2003b). In terms of its efficacy in relation to aetiology, intravitreal Triamcinolone had induced a marked improvement in macular oedema secondary to diabetic retinopathy and non infectious uveitis (Sorensen *et al.*, 2005).

1.2 BACKGROUND

1.2.1 DIABETIC MACULAR OEDEMA

Diabetic macular oedema (DME) is a general term defined as retinal thickening of the macula. All patients with diabetes are at risk of developing DME, a common micro vascular complications of the disease. Diabetic macular oedema (DME) can occur at virtually any stage during diabetic retinopathy development, and it represents the leading cause of visual impairment in people with diabetes. It is insidious in onset and painless. The severity may range from mild and asymptomatic to profound loss of vision.

1.2.2 DIABETIC MACULAR OEDEMA - EPIDEMIOLOGY

Diabetic macular oedema (DME) affects approximately 29% of diabetic patients with disease duration of more than 20 years and 20% of type 1 diabetes over a 10 year period. It responsible for a significant degree of visual loss in this population (Sutter *et al.*, 2004, Martidis *et al.*, 2002). If untreated, 20% to 30% of patients with DME will experience a doubling of the visual angle within 3 years; with current treatment, this risk drops by 50% (Fong *et al.*, 2007). In patients with type 1 diabetes, the cumulative 14-year incidences of visual impairment (VA 20/40 or worse in the better eye), doubling of the visual angle, and blindness were 12.7, 14.2, and 2.4%, respectively (Moss *et al.*, 1998). DME is a frequent manifestation of diabetic retinopathy (DR) and is a leading cause of legal blindness in

patients with type 2 diabetes. Over a 10-year period, non–clinically significant DME and clinically significant DME will, respectively, develop in 14 and 10% of Americans with known diabetes (Klein *et al.*, 1995). Approximately half of patients with DME will lose two or more lines of VA within 2 years.

1.2.3 DIABETIC MACULAR OEDEMA - PATHOGENESIS

DME occurs after breakdown of the blood retinal barrier due to leakage of dilated hypermeable capillaries and micro aneurysms. The changes in blood retinal barrier permeability and intravascular hydrostatic pressure are generally believed to be involved in the genesis of DME (Vinten *et al.*, 2007). The endothelial cells are responsible for maintaining the inner blood retinal barrier, and damage to them results in increased vascular permeability. This will results in accumulation of extracellular fluid in the macula.

The hallmark of diabetes mellitus is hyperglycaemia. Chronic hyperglycaemia is the cause of all complications of diabetes through its effect on the blood vessels which are vascular dysfunction and occlusion. Vascular dysfunction will lead to hypoxia as the natural consequences. In response to local hypoxia, affected retinal tissue will up regulate the production of growth factors, such as vascular endothelial growth factor (VEGF). VEGF is a potent angiogenic stimulus but it also induces vascular permeability. It's pro-permeability activity has been shown to be 50,000 times more potent than histamine (Ferrara *et al.*, 2003). Hypoxia also results in thickening of basement membrane of the

vascular endothelium and also in a reduction of the supportive pericytes lining retinal blood vessels. Pericytes are essential cellular components in the regulation of retinal capillary perfusion. Damages to these cells in diabetes lead to alter retinal hemodynamics. Loss of retinal pericytes represents another early features of diabetic retinopathy changes correlates with micro aneurysm formation (Gardner *et al.*, 2002).

The physics of macular oedema are governed by a pair of hydrodynamic principles, Starling's law and Laplace's law (Gardner *et al.*, 2002, Nagel and Vilser, 2004, Vinten *et al.*, 2007). The Starling's law states that the net movement of fluid and molecules across the vessel wall is determined by the interplay between luminal hydrostatic pressure, which drives fluid out of the vessel, and plasma colloid osmotic pressure, which draws fluid into the vessel. The luminal hydrostatic pressure is often increased in diabetes eyes, due to coexisting systemic hypertension and from focal retinal hypoxia. The movement of fluid out of the vessel will lead to the development of DME. The Laplace's law states that a vessel will become dilated and tortuous when the luminal hydrostatic pressure is increased. Hence, the tight junctions between endothelial cells may become disrupted and lead to fluid leakage out and tissue oedema (Nagel and Vilser, 2004, David Callanan, 2007).

1.2.4 DIABETIC MACULAR OEDEMA - DIAGNOSIS

Making the diagnosis of DME requires a careful ocular retinal examination. The optimal examination technique is biomicroscopy under stereopsis with high magnification. This

examination should be performed on all diabetic patients to avoid missing subtle and asymptomatic cases of DME. The degree of macular oedema is determined by stereoscopic fundus examination using the 78-diopter lens or 90-diopter lens. A stereoscopic fundus photograph able to detect DME and a serial photograph help in assessing the progression of the disease with or without treatment.

Macular oedema in diabetic can be divided into two subtypes focal and diffuse. Focal macular oedema derives from individual micro aneurysms or small clusters of micro aneurysms and dilated capillaries (Cunha-Vaz, 1998). Complete or partial rings of hard exudates often demarcate it. Clusters of micro aneurysms are seen in the centre of circinate exudates and fundus fluorescence angiography demonstrates both their presence and their abnormal permeability. Diffuse macular oedema is characterized by diffuse leakage from extensive areas of the posterior retinal capillary bed and a generalized breakdown of the inner blood-retinal barrier (Aroca *et al.*, 2004). The excessive vascular permeability, resulting in the leakage of fluid, lipoproteins, and other plasma constituents into the retina, leads to thickening of the retina (Verma *et al.*, 2004). It is usually symmetric in both eyes and without significant exudation.

The International Clinical Diabetic Macular Oedema Disease Severity Scale (Wilkinson *et al.*, 2003) classified diabetic macular oedema into three categories;

i. Mild - Some retinal thickening or hard exudates in the posterior pole, but distant from the centre of the macula.

ii. Moderate - Retinal thickening or hard exudates approaching the centre of the macula but not the centre.

iii. Severe - Involving retinal thickening or hard exudates involving the centre.

The other classifications of DME is based on the ETDRS (Early Treatment Diabetic Retinopathy Study) where it generally refers to the threshold level at which treatment (laser photocoagulation) is carried out. Clinically significant macular oedema (CSME) occurs if;

i. There is thickening of the retina involving the centre of the retina (macula) or the area within 500 μm of it.

ii. There are hard exudates at or within 500 μm of the centre of the retina with thickening of the adjacent retina.

iii. There is a zone of retinal thickening one disc area or larger in size, any part of which is within one disc diameter of the centre of the retina.

1.2.5 DIABETIC MACULAR OEDEMA - INVESTIGATIONS

1.2.5.1 FUNDUS FLUORESCENCE ANGIOGRAM (FFA)

Various methods of investigation are utilized to detect disruption of the BRB (blood retinal barrier) in order to determine the presence and the extent of macular oedema. Fundus fluorescence angiogram (FA) is clinically the most widely available and useful test. It is a method in which sodium fluorescence is intravenously administered followed by rapid sequence photography of the retina to evaluate its circulation.

Normally, fluorescence cannot pass through the tight junctions of retinal capillaries; however, in some disease states, such as DR and DME, dye leakage occurs. It permits study of the circulation of the retina and choroid in normal and diseased states. The amount of fluorescence leakage depends on the dysfunction of the retinal vascular endothelium. Fluorescence angiography provides enhanced visualization of the geometry and distribution of macular oedema. The method is useful in detecting early alterations of the blood-retinal barrier, capillary closure, and micro aneurysm formation. The major advantage of FA is its ability to detect macular ischemia denoted by non perfusion of the retinal capillaries and to detect subtle DME as evidenced by fluorescence leakage from the capillaries.