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

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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.

Drawbacks to use FA as a screening procedure are its invasiveness, time constraints, expensive equipment and adverse reactions. Allergic-type reactions to sodium fluorescence have been reported in patients undergoing FA, although the incidence of serious complications is rare. In general, the use of FA is limited to determining method and location of laser photocoagulation for DME and for assessing the extent of non perfusion. It has limited value over fundus photography as a diagnostic tool and is not recommended for routine use.

1.2.5.2 OPTICAL COHERENCE TOMOGRAPHY (OCT)

There are other measures used to quantify macular oedema where the retinal thickness can be measured. OCT provide images by projecting a pair of near-infrared light beams into the eye. The resulting interference pattern from these beams is dependent of the thickness and reflectivity of the retinal structures and is detected by the measuring system. The images produced appear to be cross-sections of the retina and allow the thickness of the retina to be measured. The thickness of the retina may allow DME to be followed in a quantitative manner.

1.2.5.3 RETINAL THICKNESS ANALYZER (RTA)

The Retinal Thickness Analyzer (RTA) works on the principle of slit lamp fundus biomicroscopy. It sequentially scans vertical slits across an area of the retina to generate rapidly a topographic map of retinal thickness. The reflections are captured by a black-and-white charge-coupled device (CCD) camera and stored for analysis. A bi-Lorenztian curve fitting is performed to delineate the internal limiting membrane (ILM) and retinal pigment epithelium (RPE) separation with an axial resolution of approximately 50 μm. The instrument has been used extensively in the evaluation of retinal diseases including DME. The RTA has been reported to have a high level of reproducibility.

1.2.5.4 HEIDELBERG RETINAL TOMOGRAPH II

1.2.5.4(a) Principle

Scanning laser tomography (SLT) in Heidelberg Retina Tomography II is a non-invasive technique which permits the objective, topographic measurement of the fundus. SLT employs confocal optics to attain a high resolution not only perpendicular to x and y axis

but also along z axis (the optical axis). The distribution of reflected light intensity along the optical axis for a given pixel is described as the *z*-profile or confocal intensity profile.

A new technique determines the signal width (at half peak height) and peak reflectance intensity of the *z*-profile. Studies have demonstrated a broadening of the *z*-profile signal width (SW) and a decrease in peak reflectance intensity (IN) in areas of oedema. Normalization of the reflectance values reduces the variation in intensity between successive scans; oedema $\text{index}_i = \text{SW}_i/\text{IN}_i$.

An oedema index can be derived for each pixel, which is sensitive to oedematous changes of the retina. A resultant map of these oedema indices gives a measure of the location and extent of retinal oedema. It should be noted that the oedema index is not a measure of retinal thickness but of the optical effect of oedema within the retina.

The oedema index methodology has been validated in diabetic retinopathy but not in other disease states. Change of the oedema index has been shown to correlate with change of visual function, including logarithm of the minimum angle of resolution (log MAR) visual acuity, conventional automated static perimetry and short-wavelength automated perimetry, in patients undergoing grid laser treatment for clinically significant macular oedema.

The HRT II (Heidelberg Engineering) sequentially acquires 16 two-dimensional (that is, *x*, *y* plane) confocal section images per millimetre along the optical axis (that is, *z*-axis). The oedema index analysis developed by Flanagan and Hudson has been incorporated within the HRT II as the macular oedema module (MEM). Each HRT II scan consists of 3 sequential 15° x 15° topographic images of the retina that are averaged to display a mean topography image. The mean topography image that is subsequently analyzed has a resolution of 384 x 384 pixels. Patient with astigmatism more than one dioptre should be corrected with astigmatism lens during the procedure.

The average oedema index was derived for a 600-μm radius circle centred on the fovea using the MEM software (ver. 1.0.0.4). Assessors should be masked from the subject's clinical status. At least two of the three scans needed to manifest evident oedema for any one sector to be assigned as oedematous.

1.2.5.4(b) Advantages / Disadvantages

The Heidelberg Retina Tomograph II (HRT II, Heidelberg Engineering, Heidelberg, Germany) is a confocal scanning laser ophthalmoscope that allows non invasive axial imaging of the retina with a resolution of approximately 300 μm; the width of the axial intensity signal correlates well with retinal thickening. The prototype version of the HRT II

(HRT) was originally used for the examination of the optic nerve head, and its function has been extended to the investigation of the macula and, more recently, the cornea.

The reproducibility of the parameters of the optic nerve head of the HRT has been studied extensively. In terms of macula measurements, a study was done that examined the reproducibility of the topographic measurements of the macula provided by the software using the HRT. Menezes and co-workers have reported a pooled standard deviation of 36.0μm for height measurements in cyclopleged, dilated eyes and a pooled standard deviation of 2.2μm when relative differences were calculated.

The clinical version of the HRT (HRT II) incorporates automations, which make the instrument more accessible to clinicians over the previous generation of this technology. The clinical importance of this instrument in determining small changes in retinal thickness of macula diseases such as DME depends strongly on the repeatability of its measurements.

1.2.6 DIABETIC MACULAR OEDEMA - TREATMENT

1.2.6.1 LASER PHOTOCOAGULATION

The ideal treatment for DME is primary prevention. The Diabetes Control and Complications Trial (DCCT) study showed that intensive treatment reduced the risk of retinopathy developing or progression to clinically significant degrees by 34% to 76% compared with conventional treatment. The gold standard of diabetic macular oedema (DME) treatment is macular laser photocoagulation, the benefit of which was demonstrated in the Early Treatment Diabetic Retinopathy Study (ETDRS) (ETDRS, 1985).

1.2.6.1(a) Principle

The mechanism of laser photocoagulation is thought to induce proliferation of both the endothelial cells in retinal capillaries and pigment epithelial cells, thereby improving the efficacies of both inner and outer blood–retina barriers. However, patients had only minimal visual improvement after laser treatment, and <3% had visual improvement of ≥3 lines at 3 years. Moreover, 12% of eyes developed moderate visual loss at 3 years despite treatment, and 40% of eyes with retinal thickening involving the central macula had persistent oedema at 12 months (ETDRS, 1985).

Laser photocoagulation became the standard of care in the treatment of DME primarily as a result of the findings of the ETDRS. In general, green wavelength is employed. Other wavelengths have also been utilized; while they may be advantageous in specific cases, there is no evidence that the choice of wavelength impacts visual outcomes.

The green wavelength is readily absorbed by haemoglobin, which has the advantage of improved uptake when photocoagulating micro aneurysms but may limit its uptake at the level of the retina in eyes with mild or moderate vitreous haemorrhage. In such cases, red or infrared wavelengths, provided by krypton or diode lasers, may be more efficacious and have the benefit of passing more easily through media opacities such as cataracts. In addition, longer wavelengths, such as the 810-nm diode, may be better suited for treatment of diffuse macular oedema close to the fovea centre, because they can produce deep burns while sparing the inner neurosensory retina, minimizing the risk of perifoveal scotomas.

Laser photocoagulation may work through its absorption by melanin granules in the retinal pigment epithelium (RPE) and choroid and also by haemoglobin especially in micro aneurysms. The used of laser photocoagulation results in significant improvement of oxygen supply to the inner retina directly from the choroid, which eventually reduces neovascularisation. Micro aneurysms, the sources of leakage in DME, are targeted by the laser, and haemoglobin in the micro aneurysms absorbs the laser energy. This promotes thrombosis within the micro aneurysm, halting further leakage.

There are two types of laser treatment in the macula; focal and grid laser photocoagulation. Focal treatment applied the laser directly on to the micro aneurysm, while the grid laser usually done for a diffuse oedema lasers the oedematous retina in grid pattern. Focal/grid laser setting uses laser spot of 50-100 micron and duration of 0.05-0.1 seconds. A space of one burn width was left between each grid lesion. The laser burn intensity should be light gray in colour. The area of 500 micron around the fovea is always spared.

1.2.6.1(b) Complications

Complications of macular laser treatment include paracentral scotomas, lateral creep of juxtafoveal laser scars into the fovea, accidental foveal photocoagulation, subfoveal fibrosis, and choroidal neovascularisation at the sites of laser scars. In addition, there can be residual massive hard exudates after the resolution of oedema, and patients often experience colour vision impairment (Bandello *et al.*, 2003, Tranos *et al.*, 2004).

1.2.6.2 TRIAMCINOLONE ACETONIDE

1.2.6.2(a) Mode of action

The rationale for the use of corticosteroids in the treatment of diabetic macular oedema follows from the observation that the breakdown of the blood retinal barrier leads to the oedema and is in part mediated by VEGF. Corticosteroids have been shown to inhibit VEGF and other cytokines and growth factors, thereby regulating endothelial cell tight junctions. In addition, they inhibit prostaglandin and leucotriene synthesis, which results in a local reduction of inflammatory mediators. The resultant anti-inflammatory effect contributes to the reduction of oedema. Increased diffusion by modulation of calcium channels could also account for the efficacy of the corticosteroids in reducing macular oedema.

Animal studies have shown that glucocorticoids reduce blood–retinal barrier permeability, an event that was accompanied by an apparent reduction in retinal vessel diameter (Vinten *et al.*, 2007, Wilson *et al.*, 1992). However, no study has been conducted to assess the effects on these parameters in human patients with DME. Another animal study showed that intravitreal Dexamethasone improve DME through inhibition of leukostasis. It decreased intercellular Adhesion Molecule-1 (CAM-1) mRNA and protein levels (Tamura *et al.*, 2005).

Intravitreal corticosteroids were initially considered after animal studies showed that dexamethasone phosphate injected into the vitreous was not toxic to the retina. Shortly after these animal studies, the first published reports of human intravitreal injections of corticosteroids were used for treatment of diabetic macular oedema, in 2001 (Jonas and Sofker, 2001), and for macular oedema secondary to central retinal vein occlusion, in 2002 (Greenberg *et al.*, 2002). Prior to the introduction of corticosteroids into the vitreous cavity, high doses of systemic corticosteroids were needed in the treatment of macular oedema, particularly inflammatory cystoids macular oedema (CME).

Oral steroids, unfortunately, can cause a spectrum of systemic side effects, including osteoporosis, cushingnoid state, adrenal suppression and exacerbation of diabetes. Intravitreal delivery of corticosteroids has allowed many posterior segment diseases to be locally treated without the adverse systemic side effects. Intravitreal delivery also allows the steroid to bypass the blood–retinal barrier, leading to a more concentrated dose of steroid for a prolonged period of time.

1.2.6.2(b) Pharmacokinetic

Triamcinolone Acetonide (TA) is designated chemically as 9-fluoro-11b,16a,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone and the empirical formula is $C_{24}H_{31}FO_6$ (Jermak *et al.*, 2007).

The half life of Dexamethasone phosphate in vitreous fluid was reported as three hours; hence other synthetic corticosteroids were evaluated for intravitreal use. In a subsequent study, Tano *et al* selected a more lipophilic corticosteroid, triamcinolone acetonide (TA), which has a longer residence time within the eye (Tano *et al.*, 1980).

In a study addressing the pharmacokinetics of TA after intravitreal injection, Bakri *et al* demonstrated that a 4-mg dose, in a non-vitrectomized human eye, maintains measurable concentrations for approximately 3 months (Bakri and Beer, 2004). A larger, 25-mg intravitreal dose of TA was reported to be found in the aqueous humour of a human eye up to 6 months post-injection.

An animal study was performed on TA to determine the effects of the drug on the swelling of retinal ganglion and Muller glial cells (Uckermann *et al.*, 2005). The study concluded that TA has no effect on the swelling of ganglion cells but it reversed the osmotic swelling of Muller glial cells in the retina of the rat. The inhibitory effect on the cytotoxic swelling of glial cells may contribute to the fast oedema-resolving effect of intravitreal TA observed in human patients .

Although most clinical experience with intravitreal corticosteroids has been with TA, there are other corticosteroids being considered for the treatment of macular oedema (e.g., dexamethasone, fluocinolone acetonide).

1.2.6.2(c) Pharmacodynamic

Schindler et. al. 1982 studied the clearance of intravitreal Triamcinolone and found out that the rate of intravitreal triamcinolone acetonide disappearance depended on the presence or absence of the lens and vitreous (Schindler *et al.*, 1982). Normal control eyes had the longest retention of steroid, an average of 41 days and eyes that were post vitrectomy cleared the steroid in an average of 17 days.

1.2.6.2(d) Complications and adverse effects

Injection of corticosteroid, triamcinolone acetonide has become a popular treatment recently. Triamcinolone acetonide has been reported to be effective in the management of macular edema as it suppresses inflammation, reduces extravasation of fluid from leaking blood vessels, inhibits fibrovascular proliferation, and down-regulates production of VEGF. Triamcinolone can be administered by several routes including periocular and posterior subtenon injection, however intravitreal route is preferred as it can convey the drug directly to the retina and duration of effect is longer.

The IVTA procedure is not without complications. Serious complications that could occur due to the injection are glaucoma, cataract, endophthalmitis, and pseudoendophthalmitis.

Pseudoendophthalmitis occur if a 30-G needle is used instead of a 26-G needle, which causes a partial jamming due to the crystalline steroid in the barrel of the needle as the injection is given. This results in spraying of the drug into the vitreous at a high velocity, causing a pseudo-endophthalmitis like reaction. This can be differentiated from true endophthalmitis by virtue of the immediate nature of visual loss, lack of pain, swelling and anterior segment reaction, as well as a spontaneous resolution without antibiotic therapy, all of which are not consistent with an infectious process.

An alternative hypothesis is that pseudo-endophthalmitis could be caused by an acute reaction to the vehicle of the drug. This has been suggested since the vehicle contains 6.9 mg sodium chloride for isotonicity, 15 mg benzyl alcohol as a preservative, 7.5 mg carmellose sodium and 0.4 mg polysorbate 80. However, the vehicle is reported to be well tolerated by rabbit eyes (McCuen *et al.*, 1981). This pseudo-endophthalmitis like reaction is commoner in vitrectomised and pseudophakic eyes wherein the relatively unicameral nature of the eye allows an easy access of the triamcinolone to the ocular structures leading to a brisk immune response. Apart from the above complications, there are complications one has to aware of that inherent to the procedure itself, vitreous haemorrhage and retinal detachment.

Post procedure some patients will complaint of floaters and transient blurring of vision. It happens because the drug assumes a dependant position over the macula, hence causing floaters and poor vision. Patient should be make to sit up immediately after the injection

and continue maintaining the erect posture for the next six hours at least to avoid those thing from happened.

The incidence of endophthalmitis following IVTA injection in one multicenter series was 0.87% (Moshfeghi *et al.*, 2003). The risk of endophthalmitis is increased due to the invasive nature of the procedure and the immunosuppressive effect of the injected corticosteroid. It is therefore important to use a fresh bottle for each patient to prevent endophthalmitis due to contaminants in the vial. It would be worthwhile noting down the lot number of the steroid vial in a register to facilitate tracing and culturing the bottle for contaminants if endophthalmitis occurs. Prompt intravitreal injection of antibiotics following a vitreous tap at the first suspicion of endophthalmitis should be carried out.

Intra ocular pressure (IOP) should be checked at six and 24 hours after injection and all follow up visits. Indirect ophthalmoscopy to check for central retinal arterial pulsation should be done at the end of the procedure. If the IOP is felt to be high after injection, a paracentesis may help reducing the pressure. Some surgeons aspirate 0.1 ml of vitreous to prevent the IOP rise and then remove the syringe alone with the needle still inside the eye. Triamcinolone Acetonide of 0.1 ml is then injected with another syringe introduced into the same needle. However from previous study, raised IOP is a transient phenomenon and it is controlled by anti glaucoma (Massin *et al.*, 2004).