Original Article

Intravitreal Triamcinolone For Refractory Diabetic Clinically Significant Macular Oedema

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Objective: To determine long term effects on final visual outcome, macular fluorescein leakage and intraocular pressure after intravitreal injection of triamcinolone for treating refractory diabetic clinically significant macular oedema (CSMO).

Material & Methods: Patients with CSMO of more than 12 months duration, diagnosed according to ETDRS criteria were recruited. All patients had at least two or more macular grid laser treatment with the more recent laser at least 3 months prior to the injection. Patients with CSMO and active proliferative disease, vein occlusions and macular ischemia were excluded. Patients with pre-existing significant cataract or glaucoma were also not considered. Triamcinolone, 4mg was injected through the pars-plana, infrotemporally using a 27 guage needle. The response to the treatment was monitored at 1 month, 3 months and 6 months. Visual acuity was assessed by LogMAR units, Fluorescein leakage by measuring the area of late phase of digital fluorescein angiogram and intraocular pressure by Goldman's applanation tonometry.

Results: Fourteen eyes of 13 patients were included in the study. The mean age was 68 years. All patients had an average of 2.4 previous sessions of grid laser treatment for CSMO. The mean visual acuity improved from 0.54 LogMAR units prior to the injection to 0.43, 0.40 and 0.37 LogMAR units at 1,3 and 6 months post-injection. This showed a statistically significant p-values of 0.042, 0.013 and 0.002 respectively. The mean intraocular pressure (IOP) increased from a pre-injection value of 16.57 to 19.42, 22.07 and 21.50 at 1,3 and 6 months post injection respectively. The p-value for this rise in IOP was also statistically significant at 0.035, 0.005 and 0.000 respectively. Evaluated subjectively in a masked fashion, macular post injection fluorescein angiograms of all 14 eyes (100%) were graded to show less leakage than on the pre-injection angiograms in at 1, 3 and 6 months visits. No injection site related complications were noted. No patient had a repeat injection.

Conclusion: Intravitreal triamcinolone has shown visually and anatomically encouraging results for the treatment of diabetic macular oedema that fails to respond to conventional laser photocoagulation. Raised intraocular pressure is a concern but longer follow up is needed to asses the efficacy and safety as well as need for re-treatment.

Key Words: Intravitreal triamcinolone, CSMO, Diabetes Mellitus, Retinopathy

Introduction

Clinically significant macular oedema (CSMO) is the most frequent cause of major loss of vision in patients with diabetic retinopathy.[1] Eyes with CSMO are treated with focal, grid and modified grid laser treatment depending upon the type of leakage from the capillary bed. Early treatment diabetic retinopathy study (ETDRS) demonstrated a significant benefit of focal laser photocoagulation for the treatment of this condition. Immediate focal laser showed a reduction in visual loss by 50%, however 12% of the treated eyes still suffered severe visual loss at three years follow-up.[2] This suggests that there is a definite group of patients in which laser treatment is not effective. This group has been identified as diffuse macular oedema and carries a particularly poor prognosis despite laser treatment. Various treatments have been attempted on this subgroup of patients including vitrectomy and posterior hyloid peel, internal limiting membrane peel, subtenon's, sub-conjunctival as well as intravitreal triamcinolone injections. We decided to treat this sub-group with intravitreal triamcinolone injection.

Material & Methods

14 eyes of 13 diabetic individuals were recruited to this study. All had CSMO according to ETDRS criteria, two or more previous macular laser treatment with the most recent laser at least 3 months before enrollment. Patients with CSMO and active proliferative disease, vein occlusions and macular ischaemia were excluded. Patients with preexisting

significant cataract or glaucoma were also not included.

Intravitreal Triamcinolone was offered to treat the macular oedema. Informed consent was taken from all patients. Pre-injection best corrected visual acuity and intraocular pressure were recorded. All patients underwent a pre-injection fundus fluorescein angiogram.

Surgical technique

Topical anaesthesia was applied and the eye was prepared with 5%Povidine iodine. Subconjunctival lignocaine 2% was injected at the pars plana level. 4 mg of triamcinolone acetonide was injected in the infrotemporal quadrant of the globe under direct vision with indirect ophthalmoscope. This technique also enabled to confirm the optic nerve perfusion at the end of the procedure. After the injection, the patients were asked to sit up and to keep an upright position for at least 4 hours to prevent the triamcinolone crystals from settling down on the macula. Post-injection IOP was checked 1 hour after the injection.

Follow-up

The anatomic and functional response to the treatment was recorded at 1 week, 1 months, 3 months and 6 months post injection. Functional response was judged by measuring LogMAR visual acuity and near visual acuity.The anatomic response was assessed by changes in fluorescein leakage in the late phase of Fluorescein angiogram (FFA). Potential injection related and steroid related complications were also assessed.

Results

The mean age of the patients was 67.5 years. All patients had non-proliferative diabetic retinopathy (NPDR) of maturity onset.

All patients had an average of 2.4 previous sessions of macular laser treatment for CSMO. The mean visual acuity improved from 0.54 LogMAR units prior to the injection to 0.43, 0.40 and 0.37 LogMAR units at 1,3 and 6 months post injection **(Table 1)**. No eye lost vision from baseline till 6 month follow up. Statistical analysis was done using paired t-test. This showed a standard deviation of 0.173, 0.172, 0.153 and a statistically significant p-values of 0.042, 0.013 and 0.002 for 1, 3 and 6 months post-injection respectively **(Table2).**

The mean intraocular pressure (IOP) increased from a pre-injection value of 16.57 to 19.42, 22.07 and 21.50 at 1, 3 and 6 months post injection respectively. Six patients had an IOP above 21 at 6 months, five of which were above 25. Only one patient had an IOP of 30 which was then controlled by anti-glaucoma drops. No other patient was treated for raised IOP. Paired t-test analysis showed a standard deviation of 4.55, 4.38 and 4.12 and a statistically significant p-value at 0.035, 0.005 and 0.000 respectively.

Evaluated subjectively in a masked fashion, macular post injection fluorescein angiograms of all 14 eyes (100%) were graded to show less leakage than on the pre-injection angiograms in at 1, 3 and 6 months visits. No injection related complications like endophthalmitis (infectious or sterile), retinal detachment or worsening of diabetic retinopathy was noted. No patient had repeat injection.

Discussion

Diabetic macular oedema results from the breakdown of the inner and outer blood retinal barriers leading to both intra and sub-retinal accumulation of fluid. The exact pathogenesis of macular oedema is still not fully known but it is well established that prostaglandins and vascular endothelial growth factor (VEGF) are directly involved. Steroids inhibit the prostaglandins by their effect on arachidonic acid pathway.[3,4] They also down regulate the production of VEGF and hence stabilize the blood retinal barrier,[4] hence the

Table-1: Pre-injection and Post injection LogMAR (Mean) Visual Acuities.

Pre-Injection	1 Month (Post Inj)	3 Months (Post Inj)	6 Months (Post Inj)
0.54 LogMAR	0.43 LogMAR	0.40 LogMAR	0.37 LogMAR

Table-2: Post-injection visual acuities. Standard deviation (SD) and statistically significant p-values.

	1 Month	3 Months	6 Months
SD	0.173	0.172	0.153
P-value	0.042	0.013	0.002

Table-3: Pre and post-injection IOP's (mmHg)

Pre-Injection	1 Month (Post Inj)	3 Months (Post Inj)	6 Months (Post Inj)
16.57	19.42	22.07	21.50

Table-4: Post-injection IOP. Standard deviation and statistically significant P-values.

	1 Month	3 Months	6 Months
SD	4.55	4.38	4.12
P-value	0.035	0.005	0.00

reason for using them in our study.

Steroids have been used in various ocular conditions. Topical application is sufficient for anterior segment disorders but does not deliver adequate drug to the posterior segment. Sub-tenon and retrobulbar routes need to diffuse across the sclera and choroid coupled with highly variable rate of steroid dissolution. Oral prednisolone delivers effective levels of steroids but subjects the patient to systemic side effects. Intraocular injection of triamcinolone delivers the drug to its target tissue in the most direct fashion without extraocular side effects.[5]

Triamcinolone acetonide is an effective agent for intravitreal injections in conditions that require long-term steroid administration such as posterior uveitis[6] and macular oedema of various aetiologies. Intraocular triamcinolone is non-toxic in rabbit eye as demonstrated by McQuin et al.[7] It has been successfully used in the past for the treatment of posterior uveitis and macular oedema of various aetiologies like proliferative vitreo retinopathies, choroidal neovascularization,[8] pre-retinal and optic nerve head neovascularization and as adjunctive treatment in proliferative diabetic retinopathy.[9] Triamcinolone is minimally water-soluble steroid injection in suspension form. The decreased water solubility contributes to its prolonged duration of action. Animal studies have also shown that after intravitreal injection of triamcinolone, the drug reduces the breakdown of BRB, has a vitreous half-life of 1.6 days[24] and maintains a depot lasting 21 to 41 days.[10,11] This contrasts to a half-life of only 2.5 hours for dexamethasone.[11]

Our study shows that intravitreal triamcinolone is beneficial in the treatment of diabetic macular oedema, which does not favorably respond to laser treatment. The mean visual acuity improved from 0.54 LogMAR units to 0.37 LogMAR units at 6 months. No eye lost vision from baseline at 6-month follow up. A predictable elevation of IOP above 21mm of Hg was noted in six eyes. Only one eye was treated with anti-glaucoma medication, two were kept under close observation for persistently raised IOP; in the remaining three eyes the IOP returned to normal at six months follow-up.

Jonas et al[12] and Martidis et al[3] and have shown significant benefit of intravitreal triamcinolone injections in patients with diffuse diabetic macular oedema. Karacorlu M et al[9] have raised concerns regarding elevated IOP in early post injection period which seems to normalize at 6 months follow-up.

Out study has many limitations. We had a small sample size and relatively short follow-up period. There was also no control group. It may be an idea to use a placebo control group in future studies; however the ethics of injecting a placebo drug intravitreally with all the potential risk factors may need justification.

In conclusion intravitreal triamcinolone injection has shown lot of promise in the treatment of diabetic macular oedema. We believe that it should either be contraindicated or used with great caution in patients with ocular hypertension or pre-existing glaucoma.

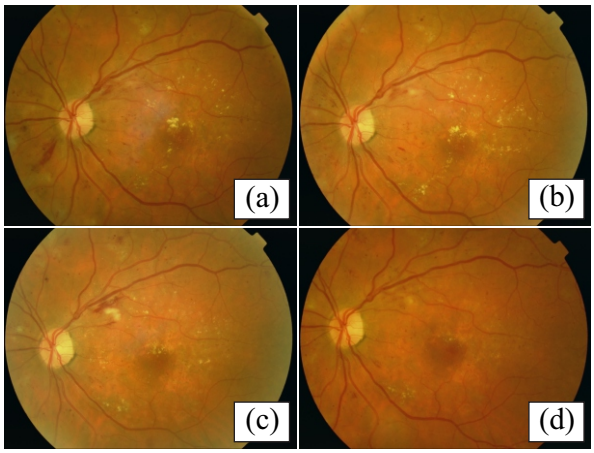

Fig1(Patient1): Time course of resolution of macular oedema(a) Pre-injection(b)1 month post-inj (c) 3 months post-inj (d) 6 months post-injection

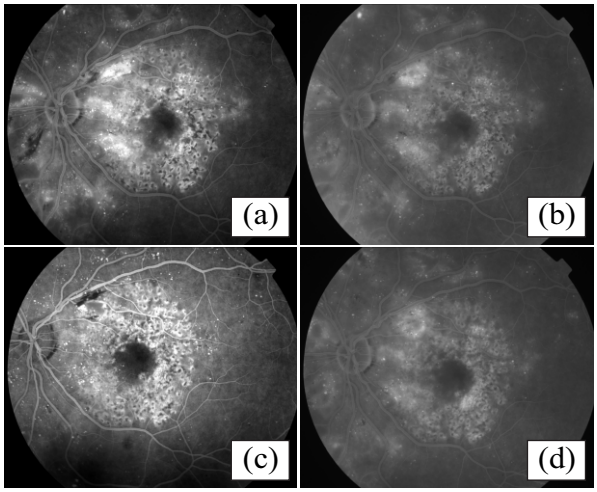

Fig-2: (Patient1) Fluorescein Angiography confirming resolution of macular oedema(a) Pre-injection(b)1 month post-inj (c) 3 months post-inj (d) 6 months post-inj

Conclusion:

Intravitreal triamcinolone has shown visually and anatomically encouraging results for the treatment of diabetic macular oedema that fails to respond to conventional laser photocoagulation. Raised intraocular pressure is a concern but longer follow up is needed to asses the efficacy and safety as well as need for re-treatment.

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