Intraocular Pressure Following Intravitreal Injection of Triamcinolone Acetonide

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Background: To investigate the intraocular pressure (IOP) response following intravitreal injection of triamcinolone acetonide (IVTA).

Design: Retrospective.

Setting: Department of Ophthalmology, Maidstone Hospital.

Method: Retrospective non-comparative case study which included 41 patients (52 eyes) (19 male, 22 female, mean age 64.1 ± 13.44; range 22 – 85 years) with progressive exudative age-related macular degeneration ARMD (n = 10 eyes) or diffuse diabetic macular oedema (42 eyes). The patients received one or more intravitreal injection(s) of 4 mg triamcinolone acetonide.

Result: IOP increased significantly (p<0.001) from 16.08 (±3.28) mmHg (range 12-26 mmHg) preoperatively to a mean maximum of 26.1 (±11.79) mmHg (range 15-80 mmHg) postoperatively (p<0.001). An IOP rise to values higher than 21 mmHg was observed in 28 (53.8%) eyes. Elevation of IOP occurred 7.5 weeks (±7.07) after the injection. In all but one eye, IOP could be lowered to the normal range with topical medication without development of glaucomatous optic nerve head changes. In the eye with an elevation of IOP to 80 mmHg, an anterior chamber tap was performed resulting in an effective reduction in pressure to 21 and then to a final IOP of 12. All five patients (11.9%) with a family history of glaucoma developed an IOP rise above the mean maximum level.

Conclusion: After intravitreal injections of 4 mg of triamcinolone acetonide, an IOP elevation greater than 21 mmHg developed in 53.8% of eyes, starting on average 7.5 weeks after the injection.

In 98.1%, IOP was normalised by topical medication alone 6 months after the injection. A family history of glaucoma may predispose patients to a greater than average IOP rise following IVTA.

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As the clinical application of intravitreal triamcinolone (IVTA) evolves, so does the interest in its potential side effects and safety. IVTA is effective when used for the treatment of cystoid macular edema caused by diabetic maculopathy, central retinal vein occlusion, uveitis and post cataract surgery macular oedema\textsuperscript{1-3}. IVTA can be considered as a therapeutic approach for a large spectrum of clinical conditions; knowledge of the subsequent IOP response needs to be established, since steroids are associated with IOP increase\textsuperscript{4}.

Currently, there has not been a demonstrable long-term toxic effect of intravitreal triamcinolone injections. However, one recognized and established side effect is the elevation of intraocular pressure (IOP) leading to a secondary chronic open angle glaucoma. A steroid induced glaucoma may occur in up to 52\% of eyes after triamcinolone injection\textsuperscript{4}.

The exact pathophysiology of steroid induced glaucoma is not entirely understood. The elevation in intra-ocular pressure is thought to be due to increased resistance to aqueous outflow by accumulation of a glycosaminoglycan protein in the trabecular meshwork resulting in an outflow obstruction. At present, this is a controversial area and not scientifically substantiated. Indisputably however, a rise in IOP following intravitreal steroid injection does occur, and this has been demonstrated by many studies\textsuperscript{4-8}. A greater understanding of the dynamics of this elevation, including its timing and extent, is necessary to enable clinicians to detect an IOP rise early and to initiate prompt treatment to prevent permanent damage to the optic nerve head.

Most of the previous studies were from centres in mainland Europe and USA, and we have complemented these with a British study from a large centre in the South-East of England with a predominantly Caucasian population.

The aim of this study is to investigate the intraocular pressure (IOP) response following intravitreal injection of triamcinolone acetonide (IVTA).

**METHOD**

This is a retrospective interventional study, which included 41 patients (52 eyes) (19 men, 22 women, 21 right eyes, 31 left eyes). Patient consecutively received one or more injections of 4 mg intravitreal triamcinolone in topical anesthesia and had a minimal follow-up of three months. All patients were Caucasian. The injection was given to patients who had reduced visual acuity due to either exudative macular degeneration with subfoveal neovascularization (n = 10 eyes) or diffuse diabetic macular edema (n = 42 eyes). Eleven patients (11/41) received the intravitreal cortisone injection in both eyes, with a time interval of 1 to 6 months between the injections. Mean age was 64.07 years (range 22-85; median 53.5 years). All patients were fully informed about the potential side effects of the therapy and signed an informed consent.
Two patients (0.05%) had primary open angle glaucoma (POAG) before inclusion into this study. Arterial hypertension was present in 10 patients (22.7%). None of the patients in the study had a history of an elevation of IOP during topical or systemic treatment.

All patients received an intravitreal injection of 4 mg of crystalline triamcinolone acetonide in 0.1 ml Ringer’s solution in the minor operating theatre. The solution was prepared by the hospital’s pharmacy removing the solvent agent. The injection was administered transconjunctivally under topical anesthesia with G. Amethocaine 1% after a paracentesis had been performed to decrease the volume of the globe. Using applanation tonometry, IOP was determined before, and at intervals of 2-4 weeks after the injection.

The mean follow up time for the patients was 7.23 (+/-2.11) months with a minimum of one month after the first injection. Anti-glaucomatous topical medication was initiated if ocular hypertension occurred (i.e. if a pressure reading above 21 mmHg was measured).

The data was analyzed using an unpaired t-test. For interindividual comparisons, only one randomly selected eye per patient was taken for statistical analysis. For intraindividual comparison, the four patients with both eyes treated were included in the analysis.

RESULT

Intraocular pressure increased significantly (p<0.001) from 16.08 mmHg (range 10-26 mmHg) to a mean maximum of 26.1 (11.79) mmHg (range 15-80 mmHg) postoperatively (figure 1). The differences between the IOP measurements before the injection and the postoperative examinations were significant (p <0.05), performed one week or later after the injection.

Figure 1: Scatter Plot of Initial IOP versus Maximum IOP Following IVTA
A rise in IOP to values higher than 21 mmHg was observed in 28 (53.8%) eyes. The elevation usually occurred after 7.5 weeks (+/-7.07).

One of the two patients with a current diagnosis of POAG demonstrated an IOP rise warranting treatment, the other needed no additional treatment.

The post-injection rise of IOP to values higher than 21 mmHg was statistically independent of sex (p=0.37). The presence of diabetes mellitus however, demonstrated a marked influence on the rate of a postoperative elevation of IOP (p=0.05).

Within the group of patients with a postoperative rise of IOP, in all but one eye, IOP could be lowered to normal levels with topical medication alone without developing glaucomatous optic nerve head changes (figure 2).

**Figure 2: Scatter Plot of the Initial and Final IOP**

One eye developed an elevation of IOP to 80 mmHg following IVTA. An anterior chamber paracentesis was promptly performed resulting in an effective reduction in pressure to 21 and then to a final IOP of 12.

All eyes which developed a secondary ocular hypertension after a second intravitreal injection of triamcinolone acetonide had also shown a rise in IOP after the first intravitreal injection. In the absence of a pressure rise after the first injection, no eyes showed an increase in IOP after the second injection.

Eight (80%) of the ten patients who received an intravitreal injection of triamcinolone acetonide into both eyes with a time interval of 3.5 to 6 months between the injections, developed ocular hypertension in both eyes at about the same time after the injection (mean 6.7 weeks).
All five patients (11.9%) in the study with a positive family history of glaucoma developed an IOP rise above 21 mmHg.

DISCUSSION

The findings of this study from a predominantly Caucasian population concur with previous studies from Europe and USA\textsuperscript{4-8}.

One of the major side effects of intravitreal injection of triamcinolone is steroid induced elevation of IOP\textsuperscript{5,9,10}. The mechanism by which this happens is not completely understood. It is postulated as follows: immediately after the injection, there is an expansion of eye volume and a corresponding increase in the rigidity of eye, as demonstrated by the Friendenwald Equation\textsuperscript{11}. One week to two months following the injection, in 40% of patients, the increased resistance is thought to be due to a change in morphological and mechanical changes in the trabecular meshwork and most IOP changes return to baseline within 3-5 months. In 1% of patients, IOP fails to return to baseline, and although filtration surgery is popular, some treat the cause rather than effect and advocate vitrectomy for uncontrolled IOP\textsuperscript{12}.

The result of the present study showed that a rise in IOP to values higher than 21 mmHg can be expected to occur in 53.8% of eyes. This is comparable to the results found from other large studies\textsuperscript{4,7}.

A predictive factor for the rise in IOP may have been the presence of glaucoma before the injection. However, there were not enough cases with underlying POAG to study the statistical significance of this properly. Other parameters such as gender did not show a marked influence on frequency and amount of elevation of IOP. The presence of diabetes mellitus demonstrated a marked influence on the rate of a postoperative elevation of IOP (p<0.05).

It is important that in all but one eye, the IOP could be controlled by topical anti-glaucoma treatment, or returned to normal values after the intravitreal steroid crystals had resolved, about 6 months after the injection. Furthermore, it is important to note that a rise in IOP after a second intravitreal injection did not occur if there was not one found after the first.

Unexpectedly, three of the patients who received intravitreal steroid injections in both eyes had an IOP rise above 21 mmHg in one eye only. The reason for this is not clear.

The dose of steroid used in the present study was the same as used in other clinical studies acetonide\textsuperscript{1,2,11,13-19}. As expected, the incidence of IOP rise was found to be similar to these studies. Jonas et al found the incidence of IOP rise to be 50% following a dose of 25 mg triamcinolone acetonide and the IOP was controlled following treatment without the development of major damage to the optic disc\textsuperscript{10}. This finding is comparable to other studies which used a lower of dose of 4 mg of IVTA. IOP is thought to be a linear dose-dependent as demonstrated by the Friendenwald equation; the precise
mathematical relationship between steroid dose and subsequent IOP response over time is yet to be determined\textsuperscript{11}.

The etiology of steroid induced glaucoma is not entirely understood. There is some evidence to suggest that the accumulation of glycosaminoglycans or increased production of trabecular meshwork induced glucocorticoid response (TIGR) protein may be responsible for this. However, in a study by Kee et al there was found to be no relation between the TIGR gene and steroid induced glaucoma\textsuperscript{6}. None of the patients in the study with steroid induced glaucoma were found to have the TIGR gene mutation. Furthermore, a study by Fingeret et al showed that variations in the MYOC gene (the animal version of the TIGR gene) did not seem to be responsible for the development of steroid induced glaucoma\textsuperscript{20}.

In the present study, all five patients (11.9\%) with a positive family history of glaucoma developed an IOP rise above 21 mmHg. This suggests that steroid-induced glaucoma may be hereditary or family history of glaucoma may predispose the patient to higher IOP rise following IVTA.

CONCLUSION

The data from this study suggest that the intravitreal injection of triamcinolone acetonide at a dosage of 4 mg leads to a secondary ocular hypertension in about 54\% of the eyes treated. The rise in IOP is reversible at 6 months after the injection and can usually be controlled by topical hypotensive medication alone. A rise in IOP following IVTA is common and poses a strong argument in favor of treating all patients with ocular hypotensive medication both pre and postoperatively. It also underlies the importance of informing patients about this risk when consenting preoperatively. A family history of glaucoma should be elicited in all patients, as this may be a predisposition to higher IOP rise following IVTA.

Further research is required to scientifically establish the aetiology of steroid-induced glaucoma and target possible areas of prevention and treatment.

REFERENCES

17. Machemer R. Five Cases in which a Depot Steroid (hydrocortisone acetate and methylprednisolone acetate) was Injected into the Eye. Retina 1996; 16: 166-7.