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The effect of intraocular pressure lowering medications on the pressure spike associated with intravitreal injection

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Abstract

Purpose. This study investigates whether the post intravitreal injection intraocular pressure (IOP) spike is modifiable with the use of prophylactic apraclonidine and dorzolomide.

Methods. The study design is a prospective, randomized controlled clinical trial. 80 eyes undergoing intravitreal injection of anti-VEGF agent were studied. A control group (n = 42) received no IOP lowering drops, and a study group (n = 38) received topical apraclonidine and dorzolamide 30 to 40 minutes before the intravitreal injection. IOP measurements were taken in both groups using the Perkins tonometer at baseline, immediately before and after the injection, 5 minutes post-injection, and 15 minutes post-injection.

Results. Mean IOP immediately post injection in the study group compared to the control group was lower: 26.71 mmHg versus 32.73 mmHg (p=0.026). The main outcome measure was the area under the curve (AUC), reflecting the trend of IOP post injection. The AUC was lower in the study group compared to the control group (Mann-Whitney U test, p=0.046).

Conclusions. The use of prophylactic apraclonidine and dorzolamide is effective in modifying the post-injection IOP spike. IOP lowering prophylaxis may be considered in patients with a high baseline IOP.

Introduction

Among the most exciting and innovative ophthalmological advances in recent years is the introduction of intravitreal injection of anti-VEGF drugs. These drugs have been shown to be sight-saving in a variety of retinal pathologies, including exudative age-related macular degeneration and diabetic macular edema.[1-3] One of the established side-effects of intravitreal injection is a temporary rise in the intraocular pressure (IOP).[4-6] This increase has been attributed to volume expansion; however, the exact mechanism remains unclear.[7,8] Even a short-lived spike in the IOP can have potentially devastating consequences on an eye that may be already compromised in terms of its vasculature. The Royal College of Ophthalmologists recommend routinely checking that the patient can see objects immediately after the injection, to ensure that the central retinal artery is patent (http://www.rcophth.ac.uk). Routine IOP measurement before and after injection may not be necessary; however, it should be considered in certain patients at risk of having a high IOP.[9]

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Several authors have addressed the issue of prophylaxis in reducing the post-injection IOP spike. Frenkel, et al. carried out a retrospective study of 71 patients, which did not show any significant benefit of pressure-lowering medications.[10] El Chehab, et al. prospectively evaluated different regimens in 210 patients and showed a significant reduction in the pressure spike with several topical medications but not with oral acetazolamide.[11] Theoulakis, et al. reported on a series of 88 patients and found a reduction of the pressure spike after the use of brimonidine/timolol.[12] To date, no treatment regimen has been established as clearly effective and beneficial for patients undergoing intravitreal injection. Indeed, the question remains whether it is at all advantageous to use prophylactic pressure lowering medications prior to intravitreal injections, and if so, in which patients. The objective of our study was to determine whether the IOP spike is modifiable by the prophylactic use of the combination of dorzolamide and apraclonidine 1%. Both of these drugs are readily available in single dose units, which is useful in reducing the risk of infection.

Materials and Methods

A prospective, randomized controlled trial was performed between October 2011 and April 2012 in a single treatment center. Ethical approval was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals.

Eighty consecutive patients due to undergo intravitreal injection of 0.05ml of ranibizumab (0.5mg/0.05ml) for a variety of retinal pathologies were included in the study. Exclusion criteria included a history of ocular hypertension or glaucoma and intravitreal injection of agents other than ranibizumab. Only one eye per patient was included. Written informed consent was obtained from all patients.

A random number generator assigned patients to either study or control group before the injection. The control group received no IOP lowering medications. The study group received one drop of topical 1% apraclonidine and one drop of topical 2.0% dorzolamide at 30 to 40 minutes before the injection. IOP measurements were taken with the Perkins tonometer (Clement Clarke, Essex, United Kingdom) at baseline before the administration of drops (T-0). Subsequent measurements were 1 minute before injection (T-1), 2 minutes after injection (T-2), 5 minutes after injection (T-3), and 15 minutes after injection (T-4). To minimize inter-observer error, the same physician carried out all measurements for a given patient, (there were 4 such physicians over the 6-month period of data collection). Physicians were not blinded to the group of the patient. The IOP measurement technique and endpoint were clearly defined and standardized for all physicians involved prior to data collection. The identical injection technique of 0.05ml of ranibizumab was used across all cases. A sterile cotton tip was applied to the injection site to prevent subconjuctival reflux. In between IOP measurements, the tonometer was made aseptic using alcohol swabs, and then dried using sterile gauze. One drop of topical chloramphenicol was administered after each IOP measurement.

The main outcome measure was the area under the curve (AUC) with respect to ground. This method is useful for detecting possible associations between repeated measures and other variables, over several time points.[13] We calculated the AUC using a formula derived from the trapezoid formula, whereby the individual measurements used were the mean IOP values for study and control groups, and the individual time distance between the measurements was the injection-relative times.

Statistical analysis was carried out using Statistical Package for the Social Science IBM SPSS Statistics Version 18 (IBM Corporation, Armonk, New York). Data was tested for normality using the Shapiro-Wilk test and the appropriate statistical tests used to compare means—independent samples t test for parametric data, and Mann-Whitney U test for non-parametric data. A p value less than .05 was considered statistically significant.

Results

The mean age was 72 years in the study group, and 71 years in the control group. The study and control groups did not differ significantly in terms of baseline IOP, with a mean (± standard deviation) of 14.17 (± 3.82) mmHg in the study group and 13.88 (± 3.83) mmHg in the control group (p = .77).

Thirty to forty minutes post administration of IOP lowering prophylaxis (and immediately pre-injection), the patients in the study group showed a mean IOP drop of 4.09 mmHg (Figure 1, Table 1). The study group had a significantly different mean IOP of 10.08 mmHg in comparison to the control group's mean IOP of 13.53 mmHg, with a p value of .001 (Independent samples t test).

The mean IOP immediately post injection in the study group was 26.71 mmHg as compared to 32.73 mmHg in the control group. Using the mean values for study and control groups at T-1 to T-4 we constructed a curve and calculated the AUC. The values for AUC were not normally distributed (Shapiro-Wilke, p = .053), so a non-parametric test was used to compare the study and control groups (Mann-Whitney U test). The study group had a lower AUC than the control group (Mann-Whitney U test, p = .046).

A significant positive correlation was found between T-1 (IOP immediately pre-injection) and the AUC (Kendel's tau: r = 0.268; p < 0.001). Data on axial length was available for 15 patients. No significant correlation emerged between the IOP spike and the axial length (Pearson's correlation: r = -.001; p = 0.997).

In both the study and control groups, the IOP showed rapid normalization post-injection. 79 of 80 eyes had an IOP of less than 30 mmHg within 15 minutes post injection. The one patient who did not have an IOP of less than 30 mmHg within 15 minutes post injection was in the control group and achieved an IOP of 28 mmHg twenty minutes following injection.

Interval	Study Group Mean IOP ± SD	Control Group Mean IOP ± SD	Mean Difference Between Groups (95% CI)	*p* Value*
T-0 (baseline)	14.17 ± 3.82	13.88 ± 3.83	0.29 (-1.68 to 2.27)	0.769
T-1 (pre injection)	10.08 ± 3.61	13.53 ± 3.66	-3.44 (-5.32 to -1.56)	0.001
T-2 (immediately post injection)	26.71 ± 10.36	32.37 ± 9.79	-6.02 (-11.29 to -0.74)	0.026
T-3 (5 minutes post injection)	21.75 ± 8.42	24.95 ± 8.06	-2.30 (-6.61 to 2.01)	0.288
T-4 (15 minutes post injection)	13.92 ± 3.35	16.20 ± 5.76	-2.28 (-4.57 to -0.01)	0.049

Table 1

The mean IOP differed between the study and control groups at various time intervals. The time intervals are baseline (T-0), immediately before the injection (T-1), immediately after the injection (T-2), 5 minutes after the injection (T-3), and 15 minutes after the injection (T-5).

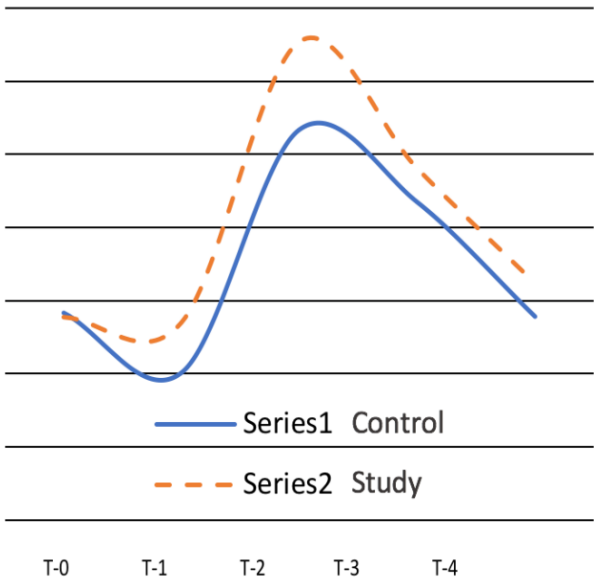

Figure 1

IOP for the control and study groups varied over time, and remained lower for the study group as compared to the case group. The time intervals are baseline (T-0), immediately before the injection (T-1), immediately after the injection (T-2), 5 minutes after the injection (T-3), and 15 minutes after the injection (T-5).

Discussion

An acutely increased IOP in an eye with compromised vasculature is one of the most hazardous perioperative complications of intravitreal injection. Prophylactic IOP lowering medications are effective in preventing IOP spikes following procedures such as ALT-trabeculoplasty and nd:YAG laser capsulotomy.[14-16] To our knowledge, this study is the first prospective, randomized controlled trial investigating the effect of dorzolamide and apraclonidine on the post intravitreal injection IOP spike.

In this study a single regimen was used: the combination of dorzolamide and apraclonidine. These agents are available in single-dose formulation and hence are a cost-effective method of reducing intraocular pressure when only a single administration is required in each patient. The extent of IOP reduction recorded with this combination is dramatic: within 30 minutes after administration of these two topical IOP-lowering agents, the IOP was reduced from 14.17 mmHg to 10.08 mmHg (approximately a 28% reduction). Such a pronounced reduction in IOP at just 30 minutes is greater than expected, and perhaps this phenomenon was due to the concurrent administration of local anaesthetic drops and their effect on corneal permeability; however, no conclusive support for this hypothesis was found in the literature.

This study suggests that a lower starting IOP pre-injection is associated with lower pressure following the injection. Glaucoma and ocular hypertension patients were excluded from this study, as inclusion may have confounded the results. Erratic diurnal IOP fluctuation is more common in eyes with glaucoma and ocular hypertension than in healthy eyes; hence, the IOP may be more likely to reach a higher peak post intravitreal injection.[17] To the patients included in this study, prophylaxis has little clinical advantage—data showed that in both study and control groups, the IOP spike was transient with the vast majority of patients returning to a pressure of less than 25 mmHg within 15 minutes post-injection. This finding is similar to that of other authors, all of whom found the IOP spike to be short lived.[4, 11, 18, 19] It is important to note that the difference in IOP between the study and control groups was less at 5 minutes and 15 minutes post injection as compared to immediately before and after injection. This finding has been reported previously in the literature,[11] though a plausible explanation for this phenomenon remains elusive.

In Frenkel, et al.'s study, the post injection IOP spike was higher than this study. This discrepancy may be partially explained by the particularly high number of glaucoma patients included in Frenkel, et al.'s study. Furthermore, some of the patients in Frenkel, et al.'s study received high volume injections, namely of 0.09 ml pegaptanib versus the 0.05 ml injection volume of ranibizumab; therefore, finding that patients who received the higher volume pegaptanib injection had generally higher IOP spikes is not surprising.

It is uncertain, though, why the post-injection IOP spike is much greater in some patients than others. Possible factors which influence the magnitude of the post-injection IOP spike include pre-existing glaucoma (excluded from this study), axial length, age, and subconjunctival reflux of syneretic vitreous and/or drug.

The magnitude of the IOP spike post-injection may be related to the axial length, since the injection of 0.05 ml into a smaller, hyperopic eye would represent a greater proportion of the total ocular volume than in a larger emmetropic or myopic eye. Data on axial length was only available on 15 of the 80 participants in this study and did not show a significant correlation between magnitude of IOP spike and axial length.

The phakic status of patients may also be a determinant of the magnitude of post-injection IOP spike, since, during intravitreal injection in phakic patients, the lens-iris diaphragm may shift forward and reduce aqueous outflow. El Chehab, et al. recorded the axial length and phakic status of patients and did not find a significant correlation between the IOP spike and either of these variables.[11]

The role of age may be considered a confounding factor. A positive correlation between ocular rigidity and age has been reported in the medical literature.[20] It is reasonable to suppose that older eyes may have less ocular compliance, and hence respond with a greater IOP spike to ocular volume increase. However, the data from this study showed no such correlation.

The strength and advantage of this study lie largely in its prospective nature. Consistent technique is used for all injections and IOP measurements, lending reliability to the findings. Limitations of this study include the limited number of patients: greater patient numbers are needed to more accurately determine the possible factors leading to adverse IOP spikes. This study is not double-blind, which allows for potential bias in the measurements.

Conclusion

This study demonstrates the effect of relatively mild IOP prophylaxis. Furthermore, this study adds to the body of evidence that prophylaxis is unnecessary in those without glaucoma or ocular hypertension who are undergoing intravitreal injection of 0.05 ml. Given current evidence that the patients with glaucoma may have greater IOP fluctuations than those without glaucoma, and that the optic nerves of glaucomatous eyes are sensitive to these IOP fluctuation, future studies should focus specifically on the magnitude, duration, modifiability and potential deleterious effects of the post-injection spike in glaucomatous eyes.[17, 21-23] A future trial could also examine the rate of visual field progression in patients with glaucoma who are also receiving serial intravitreal injections, versus those who are not.

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