



Research Article

Intravitreal Ranibizumab/ Lucentis (IVTL) injections in Glaucoma patients-Intraocular Pressure (IOP) elevation and the use of Anterior Chamber Paracentesis (ACP)

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Keywords: Age-related macular degeneration (ARMD); Glaucoma; Ocular hypertension; Ranibizumab/Lucentis; Intraocular pressure; Intravitreal injection; Anti-VEGF

Abstract

Purpose

- To assess the short term effects of intravitreal Lucentis (IVTL) on intraocular pressure in patients with ocular hypertension and glaucoma
- To determine rate of anterior chamber paracentesis (ACP) required post-injection according to departmental protocol

Methods

This was a prospective, observational study carried out between August 2011 and February 2012 in the Department of Ophthalmology, Maidstone Hospital. 24 participants (13 female, 11 male) with established ocular hypertension (OHT) or glaucoma were chosen from a cohort of patients receiving intravitreal (IVTL) Ranibizumab (Lucentis) treatment for wet age related macular degeneration (wARMD). Apraclonidine 1% was given pre-injection, and baseline IOP was measured 30 min. after this, just before IVTL. IOP was measured at baseline, within 1 min of injection, 5 min, 15 min, 30 min up to 60min following a single IVTL treatment.

Anterior paracentesis was performed if:

- Immediate post injection IOP > 50mm Hg and OHT
- Immediate post injection IOP > 40 mm Hg and there was evidence of disc damage only
- Immediate post injection IOP > 30mm Hg with evidence of disc damage and visual field loss

Results

79.2% had diagnosed disc damage and visual field loss (glaucoma); 12.5% had disc damage only (perimetric glaucoma), whereas the remaining 8.3% had no evidence of disc damage or visual field loss i.e. ocular hypertension (OHT).

Administration of Apraclonidine 1% prior to IVTL did not cause a statistically significant IOP reduction in patients with OHT and glaucoma (paired Student's t-test $P = 0.368$). Immediately post injection, mean IOP was 41.54mm Hg (SD 14.1, 95% CI 37.20 to 45.88; Paired T test results $P < 0.0001$.) which confirmed a statistically significant difference between baseline and immediate post injection IOP.

13 out of 24 (58%) of the study patients required anterior chamber paracentesis (ACP) post IVTL according to our devised protocol. There was no statistically significant difference in baseline IOP between the paracentesis and non-paracentesis groups ($p=0.4$). The presence of a bleb post injection had no statistically significant bearing on immediate post intravitreal IOP ($p=0.3$).

ACP performed at 1min restored IOP to a safer level at 5min in all cases thus treated.

Conclusion

IVTL appears to cause a significant but transient rise in IOP which is reduced after a mean time of 5 minutes. Although the clinical significance of this IOP spike is still unknown, extreme care must be taken in patients with ocular hypertension and glaucoma particularly those with established disc damage and visual field loss. Apraclonidine 1% appears to have a limited role in the prophylactic lowering of IOP pre-injection. The authors propose the use of the formulated anterior chamber paracentesis protocol for IOP management in patients with OHT and glaucoma receiving intravitreal anti-VEGF treatment.

Introduction

Vascular endothelial growth factor (VEGF) has been shown to contribute to the pathogenesis of age related macular degeneration (ARMD) and other conditions associated with choroidal neovascularisation (CNV) [1,2]. The use of anti-VEGF agents, e.g. ranibizumab (Lucentis; Novartis Pharm UK Ltd., Frimley, UK) and bevacizumab (Avastin; Genentech Inc), is recognised as effective treatment for these conditions [3]. Bevacizumab is a recombinant humanised monoclonal IgG antibody that acts by inhibiting VEGF, while ranibizumab is a humanised monoclonal antibody Fab fragment (IgG1) [4,5]. Ranibizumab is approved by NICE to treat wet ARMD. Bevacizumab is approved for use in colorectal cancer [6] and is also commonly used as an off-label treatment for ARMD [5-7].

Both ranibizumab and bevacizumab are considered safe [7-10], (CATT and IVAN studies). There are many case reports documenting transient and sustained IOP elevation after intravitreal bevacizumab and ranibizumab [11-14]. In addition, there are larger studies addressing the rate of persistent changes in IOP with intravitreal bevacizumab or ranibizumab injections [15]. This group studied the risk of IOP elevation in patients with and without pre-existing glaucoma and found that the glaucoma group was at a significantly increased risk of sustained IOP elevation following anti-VEGF injections [15].

Although, studies have investigated ways of reducing IOP elevations following anti-VEGF injections [16,17], no prospective studies on glaucoma patients are available. Also, the significance of IOP elevations, whether transient or sustained, on the long-term progression of glaucoma is unknown, although animal and human studies purely on high IOP in the past have demonstrated deleterious effects on the optic disc cupping and visual field indices [18,19].

With the knowledge that transient and sustained IOP elevations occur following anti-VEGF injections, and that glaucoma is an independent risk factor for sustained IOP elevations, we prospectively examined the IOP elevation profile following a single IVTL injection for wARMD specifically in patients with pre-existing glaucoma. We also propose arbitrarily a treatment protocol utilising anterior chamber paracentesis (ACP) for IOP elevations in glaucoma patients undergoing anti-VEGF injections according to glaucoma severity.

Methods and Materials

This was a prospective, observational study carried out between August 2011 and February 2012 in the Department of Ophthalmology, Maidstone Hospital. 24 participants (13 female, 11 male) with established ocular hypertension (OHT) or glaucoma were chosen from a cohort of patients receiving intravitreal (IVTL) Ranibizumab (Lucentis) treatment for wARMD. Severity of ocular hypertension and glaucoma was classified into three categories; disc damage and visual field loss, disc damage only and no disc damage or visual field loss i.e. ocular hypertension (Figure 1).

Within a period of two months prior to their intravitreal treatment, all patients underwent thorough ophthalmological investigations, which included determination of best-corrected Snellen visual acuity, slit lamp and fundal biomicroscopy, optical coherence tomography and fundus fluorescein angiography. OCT and FFA images were analysed by a medical retinal specialist.

On the day of their intravitreal treatment, patients with established glaucoma and ocular hypertension had the following parameters measured; baseline intraocular pressure using the Icare® tonometer, (Tiolat Oy, Helsinki, Finland) optic disc examination using slit lamp biomicroscopy and visual field assessment with Humphrey

SITA standard 24-2 perimetry. All study patients received Apraclonidine 1% and IOP was re-measured 30 minutes prior to their intravitreal injection. Patients then received 0.05mL of intravitreal Ranibizumab (Lucentis) for treatment of their wet age-related macular degeneration and it was recorded whether there was presence of a subconjunctival bleb.

Post injection, IOP was measured at the following time intervals; immediately post injection (i.e. within 1 minute), 5 minutes, 15 minutes and 30 minutes. This was continued up to 60 minutes post injection or until the reading was within 5mm Hg of the baseline IOP.

Anterior chamber paracentesis was performed if:

- Immediate post injection IOP > 50mm Hg
- Immediate post injection IOP > 40 mm Hg and there was evidence of disc damage
- Immediate post injection IOP > 30mm Hg with evidence of disc damage and visual field loss

All cases had pre-treatment with g. Chloramphenicol 0.5%, Proxymetacaine 1% and g. Povidone Iodine, one drop of each at 5 minute intervals for 15 min. ACP was performed with a 27 gauge needle on the end of an Insulin syringe, passed horizontally and inferiorly at the corneal limbus.

Statistical Analysis

The major endpoint of this study was to determine the immediate and short-term effects of intravitreal Ranibizumab injections on intraocular pressure in patients with established ocular hypertension and glaucoma. Analyses were carried out using the XLSTAT add in software for Microsoft Excel® (Addinsoft, USA) for Windows 2000. The χ^2 test was used in the comparison of nominally scaled variables whilst we employed the paired student's t-test to compare nominal variables against the mean values of measurement variables. A p-value of less than 0.05 was considered as being statistically significant.

Results

Patient characteristics

The clinical profiles of the selected patients are illustrated in table 1. There was no statistically significant difference in the mean age ($p=0.33$) or gender ($p=0.32$) between the three groups.

Classification according to disease severity

Out of the 24 patients with established ocular hypertension or glaucoma receiving intravitreal treatment, 79.2% had diagnosed disc damage and visual field loss. 12.5% had disc damage only whereas the remaining 8.3% had no evidence of disc damage or visual field loss i.e. ocular hypertension. This is illustrated in figure 1.

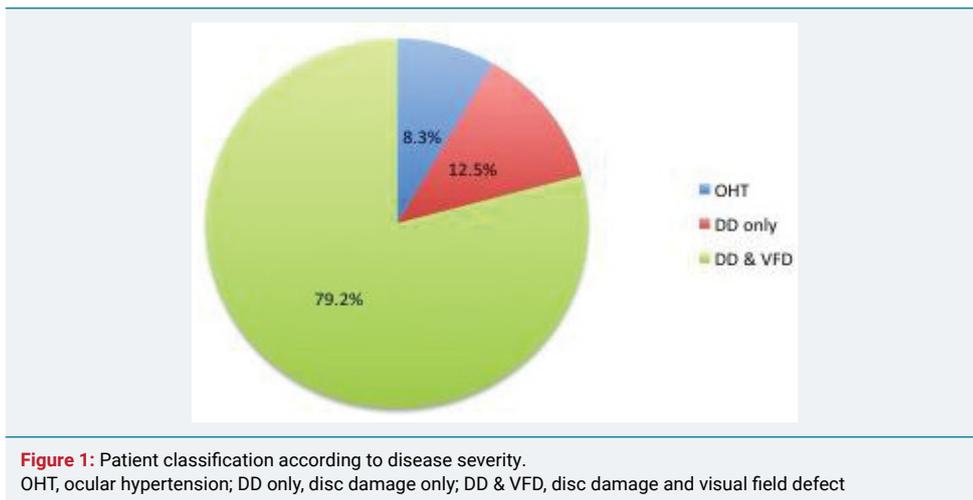
The use of Apraclonidine 1% (Iopidine)

The mean baseline intraocular pressure for all three groups was 16.92mmHg (range 9 to 28, SD=4.98). Thirty minutes after the administration of apraclonidine 1% administration, the mean intraocular pressure was 15.71mmHg (SD=4.58). The two-tailed P value was 0.3855 indicating that administration of apraclonidine 1% thirty minutes prior to intravitreal injection of 0.05mL did not cause a statistically significant intraocular pressure reduction in patients with ocular hypertension and established glaucoma.

Table 1: Characteristics of ocular hypertension and glaucoma patients.

Characteristics	OHT group (N=2)	DD only group (N=3)	DD & VFD group (N=19)	p value
Patient				
Age (in years)				0.33
Mean	68.5	78.7	75.8	
Range	60-77	73-83	60-91	
Gender				0.32
Male	2 (100%)	2 (66.7%)	10 (52.6%)	
Female	0	1 (33.3%)	9 (47.4%)	

OHT, ocular hypertension; DD only, disc damage only; DD & VFD, disc damage and visual field defect.



Immediate post injection intraocular pressure

Immediately post injection, the mean intraocular pressure across the three groups was 41.54mmHg (SD=14.1). A two-tailed $p < 0.0001$ confirmed an expected statistically significant difference between the baseline and immediate post injection intraocular pressure.

Table 2 illustrates the mean baseline and immediate post injection intraocular pressure between the three disease severity groups. There was no statistically significant difference in the baseline and immediate post injection intraocular pressure between the three.

Anterior chamber paracentesis

In accordance with our devised post injection protocol, 14 out of 24 (58.3%) of our study participants required an anterior paracentesis. There was no statistically significant difference in baseline IOP between the paracentesis and non-paracentesis groups ($p=0.247$).

Disease severity appeared to have an influential bearing on whether or not an anterior paracentesis was required with 12 out of the 14 paracentesis patients belonging the established disc damage + visual field defect group. However, the accuracy of this is difficult to ascertain owing to the small sample size (Figure 2).

The mean baseline, immediate post injection and 5 minutes post injection intraocular pressure readings are shown in figure 3. The data indicates a statistically significant immediate transient rise in intraocular pressure in both the paracentesis and non-paracentesis groups. The pressure spike appears to fall within 5mmHg of the baseline intraocular pressure in the majority of the study participants after 5 minutes post-injection. ACP performed at 1min restored IOP to a safer level at 5min in all cases thus treated

Table 2: Mean baseline and immediate post injection IOP between the three disease severity groups.

	OHT (N=2)	DD only (N=3)	DD & VFD (N=19)	P value
Baseline IOP (in mmHg)	24	14.3	16	P=0.06
Immediate post injection IOP (in mmHg)	37	31.3	41.95	P=0.379

OHT=ocular hypertension; DD only=disc damage only; DD & VFD=disc damage and visual field defect, IOP=intraocular pressure.

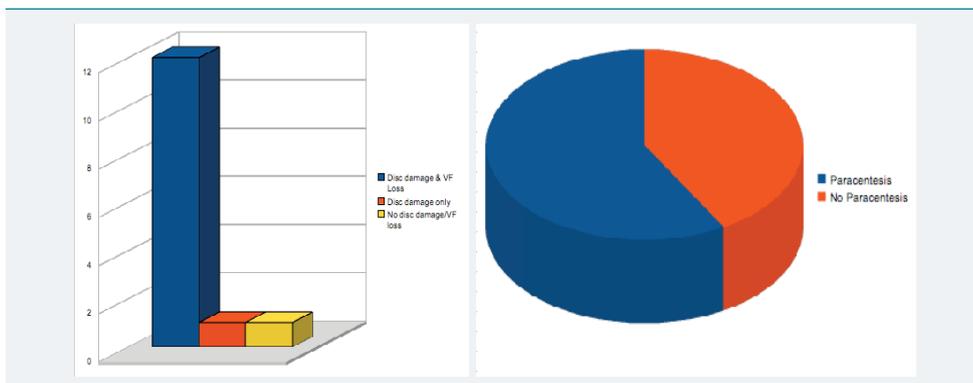


Figure 2: Patients requiring anterior chamber paracentesis & their classification according to disease severity.

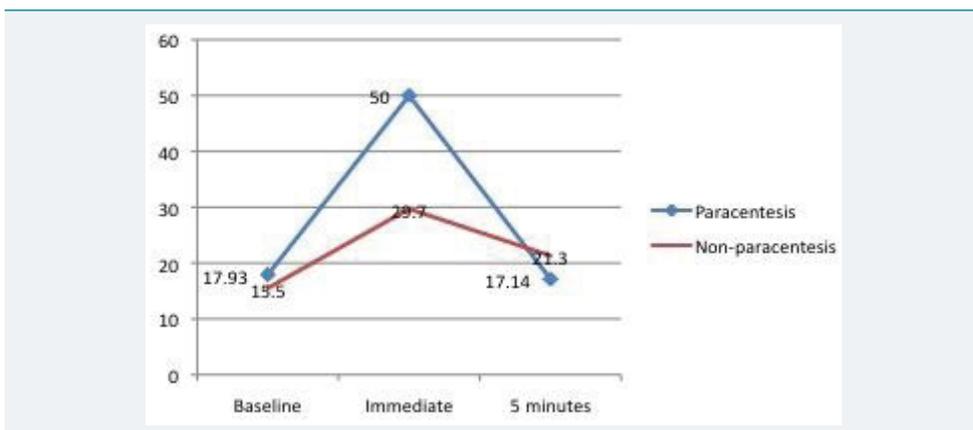


Figure 3: Mean intraocular pressure changes after the intravitreal injection of Ranibizumab (Lucentis).

Bleb presence

Out of the 24 eyes injected, the presence of a subconjunctival bleb after the intravitreal injection was noted in 4 patients (16.7%). There was no statistically significant difference (P value 0.95) in the immediate post injection intraocular pressure between patients who had a subconjunctival bleb (mean 42mmHg, SD 19.61) and those who did not (mean 41.45mmHg, SD 13.40).

Discussion

It is most pertinent to note that patients under our care often have multiple ocular co-morbidities, e.g. ARMD and glaucoma. The high volume nature of our wARMD treatment clinics means that other co-morbidities could be overlooked. Glaucoma is one of the commoner conditions and is especially important to note since any situation that leads to poor IOP control can obviously compromise the overall vision [18,19]. Therefore, we must take care not to cause deterioration of one condition whilst trying to treat another.

Studies have demonstrated not only transient but also sustained IOP elevations beyond 1 month in glaucoma patients following anti-VEGF injections [14,15,20-25].



This is of great concern since even if the pre-injection glaucoma control is satisfactory (as in our study) this could become compromised after IVTL despite continuation of the same glaucoma treatment, in up to 33% of patients. Therefore, it is most important to treat any IOP elevations in this group of patients aggressively at the outset, not only to stem the transient IOP spike, but also to prevent sustained increases in IOP.

Therefore, we investigated the IOP elevation prospectively only in patients with glaucoma (83.5%) or OHT (16.5%). The glaucoma group was further sub-divided so that there were 3 groups of patients with differing degrees of disease severity: 1. ocular hypertension only, 2. established glaucoma with disc damage only, 3. established glaucoma with disc damage and visual field loss.

Pre-treatment with Apraclonidine 1% did not affect the baseline IOP significantly at 30min. Results from one study recently were consistent with a significant pre-treatment IOP lowering effect, although at 45min, and not restricted to patients with glaucoma/OHT [17]. Therefore, our study was at odds with previous studies on this matter; it could be related to the relatively smaller sample size, and/or because our cases were exclusively glaucoma/ OHT. One study that agreed with ours found that prophylactic IOP-lowering was not effective in preventing IOP spikes post-injection, and was therefore deemed unnecessary [21]. We maintain that the IOP- lowering effect of pre-treatment with Apraclonidine 1% in glaucoma patients undergoing anti-VEGF injections remains uncertain.

We also investigated whether the presence of vitreous reflux had any significant bearing on the IOP rise following intravitreal Ranibizumab injections. This vitreous reflux/ bleb was observed in 16.7% of our study subjects although one study reported the as 33% [26]. Another study concluded that the actual absence of vitreous reflux following intravitreal injections of Ranibizumab or Triamcinolone appeared to be a determining factor in the short-term rise of IOP post injection [27]. From our study results, there was no statistically significant differences in baseline and immediate post injection IOP readings between subjects in which a subconjunctival bleb was noted and those who did not develop one.

Our study looked at the effects of intravitreal Ranibizumab only (Lucentis; Novartis) (IVTL) and therefore, there were no additional confounding factors from the use of other agents, e.g. Bevacizumab (Avastin; Genentec, Inc) which is associated with more frequent IOP elevations, with the possible causes of this having been discussed very elegantly in a previous study [28].

Transient IOP elevations have been reported in various studies that included patients with and without glaucoma [10,16,17,29]. In these studies, an IOP elevation of the order of 10mmHg or more was regarded as significant, probably because it is more than normal diurnal IOP fluctuations [30]. In this study, which concentrated purely on the OHT-glaucoma disease spectrum, the frequency of transient IOP elevation (deemed to require ACP- see figure 3) was much higher than in previous studies (58% v 30%). This probably reflects the fact that glaucoma eyes with an already compromised aqueous humour outflow system may be more prone to developing elevated IOP in this setting. The higher mean IOP in this group of patients is an indication that natural fluctuations in eye pressure are not a likely explanation for the observed values.

Based on the frequency and severity of transient and sustained IOP elevations in this group of susceptible eyes, we devised a treatment protocol involving ACP to stem the transient IOP elevation. Although the significance of transient IOP elevations is unknown, we know from previous studies that long-term tight IOP control, particularly in patients with established glaucoma (advanced disc cupping and field defects) is essential to prevent further visual field loss [19,31]. Although patients with normal uncompromised optic discs are able to tolerate short term intraocular pressure



spikes following procedures such as cataract surgery [32], there is some evidence to suggest that transient IOP spikes in patients with vulnerable optic discs are likely to be detrimental [33-36]. In one electrophysiological study the inner retina of eyes with ocular hypertension had a heightened sensitivity to vascular or mechanical changes induced by transient IOP elevation [37]. Another study on patients with glaucoma undergoing LASIK concluded that it is possible that a small cohort of patients with pre-existing glaucomatous optic neuropathy may be more susceptible to transient increase in IOP, although the result needed confirmation with more cases [38].

The mechanisms of sustained elevation of IOP by IVT anti-VEGF remain unknown. However, it may be multifactorial, involving 1) Intraocular injection-related complications, such as mechanical blockage of the trabecular meshwork or Schlemm's canal outflow 2) Drug-induced complications such as trabeculitis or uveitis and cytotoxicity to the trabecular meshwork 3) Patients with pre-existing glaucoma [39]. In a recent meta-analysis, it was also difficult to establish a link between frequency of IVT injections and sustained IOP rise [39], but one randomised controlled trial showed that the frequency of IOP elevation following IVT Aflibercept (which is injected less frequently) was lower than IVT Ranibizumab [40].

There are limitations and weaknesses of our study. The small sample size has a bearing on the statistical accuracy of the interpreted results. However, our results on the whole appeared to be in concordance with similar larger studies. In addition, this study did not take into consideration which stage of anti-VEGF treatment the patients were in or whether they had already received previous intravitreal treatment for their wet age related macular degeneration.

In summary, patients receiving intravitreal anti-VEGF treatment for wet age related macular degeneration benefit greatly from the unprecedented central vision gains in a disease, which was previously deemed untreatable. However, patients with pre-existing conditions in which the optic nerve is vulnerable, are at risk of developing further optic disc damage due to the intraocular pressure spikes after intravitreal procedures. These patients are also at a higher risk of developing sustained elevated IOP and further glaucoma-related loss of vision.

The current study confirms and adds to the data related to the growing number of cases of IOP elevation in patients receiving intravitreal anti-VEGF injections. It demonstrates that eyes with glaucoma have a higher frequency of IOP elevation in this setting, that pre-treatment with Apraclonidine 1% is of limited value in preventing this, but anterior chamber paracentesis (ACP) is a safe and very effective method for reducing the IOP to a safe level quickly. It is also quick to perform so that it does not add any additional time to the treatment procedure and does not add any significant risks to the patient. None of our cases of ACP had problems such as endophthamitis or hypotony or corneal decompensation.

Although our study was prospective in a real-world setting, advocating the routine use of ACP in this situation is not possible because of the small sample size. This study is being continued to include more cases, and further prospective studies are required to investigate whether or not the visual field indices and optic disc/ retinal nerve fibre layer in these cases deteriorate more than matched cases of glaucoma not undergoing IVTL.

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