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Intraocular pressure measurements following intravitreal anti-vascular endothelial growth factor injections with and without the use of a Honan balloon: a randomised open label clinical trial

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Abstract

Objective: To assess whether ocular compression pre-intravitreal bevacizumab injection is beneficial in reducing the post-intravitreal injection intraocular pressure (IOP).

Method: A prospective randomised, two-arm parallel control trial, at a secondary care ophthalmology clinic (Witbank Provincial Hospital) was conducted. Fifty-six patients receiving intravitreal injections of 0.1 ml bevacizumab (Avastin, Genentech, Roche, Basel, Switzerland) were randomised to either receive no intraocular pressure-lowering intervention pre-injection, or to receive intraocular pressure-lowering intervention pre-injection with the application of a Honan balloon inflated to 20–30 mmHg and applied over the eye for 15 minutes. After the administration of intravitreal injection in either group, the patients' intraocular pressures were measured at 5-, 10- and 30-minute intervals using the Goldmann applanation tonometer.

Results: Twenty-eight patients were enrolled in each of the intervention and control arms of the study. The median baseline IOPs were 14 mmHg (IQR: 11–18 mmHg) and 14 mmHg (IQR: 12–16.5 mmHg) (p=0.914) in the control and intervention group respectively. The median IOPs in the control and intervention groups at 5-, 10- and 30-minutes respectively were 36 mmHg (IQR: 33–38 mmHg) and 18 mmHg (IQR: 16–24 mmHg) (p<0.001); 29 mmHg (26–30 mmHg) and 18 mmHg (14–20 mmHg) (p<0.001); and 24 mmHg (20–26 mmHg) and 18 (12–18 mmHg) (p<0.001).

Conclusion: The results demonstrate a significant reduction in the post-injection IOP rise with the use of a Honan balloon to reduce IOP prior to the administration of intravitreal injections. Based on the findings of this study it is recommended that the Honan balloon be used prior to intravitreal injections in patients with normal pre-injection IOPs.

Key words: anti-VEGF, bevacizumab, intraocular pressure, Honan balloon, randomised clinical trial

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Conflict of interest: The authors declare that there is no conflict of interest with respect to this study.

Introduction

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents have become the standard of care for the treatment of many retinal diseases including, diabetic macular oedema (DMO) and neovascular age-related macular degeneration (nAMD).[1] Although its use intravitreally is off-label, bevacizumab (Avastin, Genentech, Roche, Basel, Switzerland) is a commonly used anti-VEGF drug which has a good safety and efficacy profile.[2–8]

Transient rises in intraocular pressure (IOP) have been documented when administering intravitreal bevacizumab; however, most patients' IOPs return to normal within 30 minutes of injection administration.[7,9] These increases in IOP carry the risk of ocular damage as primate models have shown decreased axonal transport at the optic nerve head.[10] This can result in optic nerve damage or even central retinal artery occlusion.[11] Hollands *et al.*[9] and Benz *et al.*[12] reported that only 2.9% and 10% of patients respectively had a persistent significant IOP increase of ≥25 mmHg at 30 minutes post-injection. This IOP level was deemed unsafe and thus warranted further monitoring by the investigators.[9] No long-term increase in IOP has been noted after anti-VEGF injections.[7,13]

In order to address these transient IOP increases, multiple methods have been described including medical therapy such as topical brimonidine or oral acetazolamide;[11] and mechanical methods such as digital ocular massage,[14] anterior chamber paracentesis(ACP) both pre- and post-intravitreal injection, and the Honan balloon (*Figure 1*).[15–17] Katayama *et al.* found in a randomised clinical trial (RCT) comparing topical brimonidine, oral acetazolamide (both administered 90 minutes before intravitreal injection) and post-injection paracentesis that all were effective in reducing IOP post-intravitreal injection of bevacizumab.[11] Digital massage and ACP carry the risk of endophthalmitis[17] while the medical therapy options increase time spent by patients at the outpatient clinic.

There is clinical equipoise regarding the use of the Honan balloon before the administration of intravitreal injections. Hernaez-Ortega *et al.* showed that the Honan balloon was effective in reducing the IOP in patients before intravitreal injection and did not result in central retinal artery occlusion for a median follow-up of 5.8 months.[17] An RCT by Hong *et al.* showed no difference in IOP post intravitreal injection at 3 minutes when using the Honan balloon to when it is not used.[18] We therefore decided to conduct an RCT comparing the use of the Honan balloon before intravitreal injection compared to the standard of care procedure in which no pre-injection device or therapy is used.

Methods and materials

A prospective, randomised, two-arm parallel study design, at a secondary care ophthalmology clinic (Witbank Provincial Hospital), was conducted between August 2014 and November 2014. The study was commenced after approval by the University of Pretoria Research Ethics Committee and was conducted in accordance with the tenets of the Declaration of Helsinki.

Patient eligibility and study treatment

Inclusion criteria were:

- patients 18 years of age or older
- patients who gave consent to be part of this study
- patients who required treatment with intravitreal bevacizumab (diabetic macular oedema or nAMD).

Exclusion criteria were:

- Patients who had undergone any IOP-lowering surgery, e.g. filtration surgery, or patients with a glaucoma drainage device (GDD) in situ
- Patients who had undergone intraocular surgery in the past 6 months
- Patients with a history of previous orbital surgery
- Patient with orbital diseases, e.g. Tolosa–Hunt syndrome, idiopathic orbital inflammatory disease, orbital myositis
- Patients whose IOP could not be measured within the specified time intervals of 5-,10- and 30-minutes
- Patients diagnosed with orbital tumours.

The study consisted of two groups of 28 patients who required treatment with the intravitreal injection of bevacizumab. Once informed consent was obtained, patients were randomly assigned to two groups.

Randomisation was performed using file numbers that were sequentially generated at the filing department with even and odd numbers being assigned to the experimental and control group respectively. All intravitreal injections and measurements were carried out by one investigator (HT).

The control group received their intravitreal injection using the standard of care method, whereby no pre-injection ocular compression was applied before the intravitreal administration of 0.1 ml bevacizumab. The experimental group of patients received their intravitreal injection with prior application of the Honan balloon to the eye in the supine position. The balloon was inflated to 20–30 mmHg for 15 minutes. Thereafter, the Honan balloon was removed, and administration of the intravitreal injection was performed as per the standard of care method.

After the administration of intravitreal injection in either group, the patients' intraocular pressure was measured at 5-, 10- and 30-minute intervals using the Goldmann applanation tonometer. For safety reasons all patients were followed up until normalisation of their IOPs occurred.

Sample size and statistical analysis

Statistical analysis was performed using STATA 15.1 (Statacorp, Texas USA). The sample size of 56 (28 in each arm) was calculated using a difference of 4 mmHg at 30 minutes post injection with an alpha level of 0.05 and a power of 90%. This was calculated using Satterthwaite's t-test assuming unequal variances. For all analysis, significance was set at $p<0.05$. Non-parametric continuous variables such as IOP were compared using the Wilcoxon rank sum test (Mann-Whitney test). Dichotomous outcomes between the two study groups were appropriately tested using the chi-squared or Fisher's exact tests. Multivariate logistic regression and multivariate Cox regression models were used to calculate the adjusted odds ratio and adjusted hazard ratio respectively. Kaplan-Meier curves were used to analyse time-to-event data and the log-rank test for equality of survivor functions was used to check for statistical significance.

Figure 1. Honan balloon

Results

There were 58 patients eligible for participation in the study. Two patients were not included, one because of timing difficulty (within the first 5 minutes after the injection) and another due to difficulty with positioning the patient during IOP measurement with the time period having lapsed. Fifty-six patients were therefore enrolled; 28 patients received intravitreal injections with prior application of the Honan balloon and 28 patients received injections as per the standard of care.

Baseline characteristics of patients within the two groups are shown in *Table I*. The two study groups were analysed using intention-to-treat analysis, and no secondary analysis was performed.

Table II shows the median IOP values at the three post-injection time intervals for the control and experimental groups. IOPs increased markedly 5 minutes after the injections in both groups although the control group had a much higher median IOP compared to the experimental group. Over the next 30 minutes, IOPs tended to normalise in both groups; however, at all three time intervals, the median IOP in the control group remained statistically significantly higher compared to the experimental group.

The proportion of patients with pressures below 25 mmHg post injection by group is shown in *Table III*. At all three time intervals the proportion of patients with IOPs below 25 mmHg was statistically significantly greater in the experimental group. Thirty-seven per cent (n=10) of patients from the control group and 3% (n=1) of patients from the experimental group had IOPs of more than 25 mmHg 30 minutes after the injection. *Table IV* shows the unadjusted odds ratio (15) and the odds ratio (19.5) of the IOP being below 25 mmHg at 30 minutes after adjustment for age, glaucoma and lens status. The odds of having lower IOPs is statistically significantly higher in the experimental group when compared to the control group. *Figure 2* shows the Kaplan-Meier curves for IOP<25 mmHg at 30 minutes post-intravitreal injection in both the experimental and control groups. A log-rank test performed on the Kaplan-Meier curves yielded a p-value<0.001.

From the control group, nine of the ten patients with IOPs ≥25 mmHg returned to below 25 mmHg at 120 minutes post injection. The remaining patient's IOP remained significantly elevated and required initiation of IOP-lowering medication consisting of a single dose of 250 mg acetazolamide and topical bimatoprost and timolol combination instilled daily. The patient's IOP was controlled within three days of medication and the glaucoma medication was discontinued. As for the one patient in the experimental group, the IOP had returned to below 25 mmHg at 120 minutes post injection.

Table I: Baseline characteristics of the study population

Patient characteristics	Without Honan balloon	With Honan balloon	p-value
Median age (IQR) in years	66 (61–74)	66.5 (61.5–78.5)	0.6578*
Sex n (%)			
Male	12 (43)	14 (50)	0.592**
Female	16 (57)	14 (50)	
Lens status n (%):			
Phakic	16 (57)	10 (36)	0.108**
Pseudophakic	12 (43)	18 (64)	
Median baseline IOP (IQR) mmHg	14 (11–18)	14 (12–16.5)	0.914*
Glaucoma n (%)	6 (21)	9 (32)	0.365**
Diagnosis n (%):			
Neovascular AMD	4 (14)	7 (25)	0.503†
Diabetic macular oedema	24 (86)	21 (75)	
Eye n (%):			
Right	12 (43)	15 (54)	0.422**
Left	16 (57)	13 (46)	

* Two-sample Wilcoxon rank-sum (Mann-Whitney) test
** Chi-squared test
† Fisher's exact test

Table II: Median IOPs of the two study groups at 5-,10- and 30-minutes post injection

Time post-injection	IOP	Without Honan balloon	With Honan balloon	p-value*
5 minutes	Median IOP (IQR) mmHg	36 (33–38)	18 (16–24)	<0.001
10 minutes	Median IOP (IQR) mmHg	29 (26–30)	18 (14–20)	<0.001
30 minutes	Median IOP (IQR) mmHg	24 (20–26)	18 (12–18)	<0.001

*Two-sample Wilcoxon rank-sum (Mann-Whitney) test

Table III: Proportion of patients with pressures below 25 mmHg post injection by group

Time post injection	Without Honan balloon	With Honan balloon	p-value*
5 minutes n (%)	0 (0)	22 (78.6)	<0.001
10 minutes n (%)	3 (10.7%)	27 (96.4%)	<0.001
30 minutes n (%)	18 (64.3%)	27 (96.4%)	0.005

*Fisher's exact test

Table IV: Odds ratios of having an IOP<25 mmHg in the experimental vs control group

Ratio	With Honan balloon	p-value
Unadjusted odds ratio (95% CI) of achieving IOP <25 mmHg at 30 minutes*	15 (1.8–127.6)	0.013
Adjusted odds ratio (95% CI) of achieving IOP <25 mmHg at 30 minutes**	19.5 (2.0–189.4)	0.010

* Univariate logistic regression
** Multivariate logistic regression adjusting for lens status, glaucoma and age

Discussion

Our study showed that a 0.1 ml intravitreal injection of bevacizumab was safe with respect to short-term IOP changes in patients, where pre-injection ocular compression was applied via a Honan balloon compared to patients where no pre-injection ocular pressure was applied.

Although there was a higher median IOP at 30 minutes post injection compared to baseline in both groups, the experimental group displayed a statistically significantly lower median IOP compared to the control group at all three time intervals. The median IOP in the experimental group was also within the normal range at all three time intervals indicating a better safety

profile when using the Honan balloon. This contrasts with a study by Hong *et al.*[18] who showed no difference at 3 minutes.

In the control group, 35.7% (n=10) had IOPs of more than 25 mmHg at 30 minutes post injection compared to 3% (n=1) in the experimental group. The long-term consequences of transient IOP spikes after intravitreal injections are unknown. However, the potential for negative sequelae should be considered, especially in patients with advanced glaucomatous optic neuropathy.[9] It is, however, important to consider the IOP increase during the application of the Honan balloon itself. The authors believe that this IOP increase is of a shorter duration than the sustained IOP elevation that occurred in a significant proportion (35.7%) of the control group and the benefit of the Honan balloon therefore mitigates any potential harm. Hernaez-Ortega *et al.* also showed that there were no medium-term sequelae such as endophthalmitis or central retinal artery occlusion from the use of the Honan balloon pre-injection.[17] It is, however, important to note that all baseline IOPs were controlled in both the experimental and the control groups. The results of this study should therefore be treated with caution when treating patients with uncontrolled IOP.

Using multivariate regression, and after adjusting for age, lens status and the presence of glaucoma, our study showed a significantly higher odds ratio (19.95) for achieving an IOP<25 mmHg at 30 minutes in the experimental group when compared to the control group. The Kaplan-Meier curves of both the experimental and control groups were also statistically significantly different in achieving an IOP <25 mmHg (p<0.001). To our knowledge no studies have looked at IOP for this duration after intravitreal injection using a Honan balloon.

The proportion of patients with increased IOP (≥25 mmHg at 30 minutes) in our study is higher, 35.7% in the control group, and more sustained than those found by Hollands *et al.*[9] (2.9%) and Benz *et al.*[12] (10%) respectively. It should be noted that even though no ocular compression was applied pre-injection by Hollands *et al.*, only 0.05 ml of anti-VEGF was injected (half the dose injected in our study).[9] The IOP rise seems to be dose-dependent with Benz *et al.* using a volume of 0.1 ml of triamcinolone.[12] The one patient who had uncontrolled IOP in the experimental group in our study had a small orbital aperture with deep set eyes. Due to this, the Honan balloon was supported by the orbital rim and was unable to apply sufficient pressure to the globe.

Although data was not collected to specifically assess pain and visual acuity, the investigators found that without ocular decompression before the injection, patients frequently complained of pain and temporary loss of vision. There was also more discomfort associated with the insertion of the needle and the injection, and reflux of some fluid (possibly bevacizumab or liquified vitreous) was frequently observed.

Limitations of this study include potential investigator bias that may occur since it was not a double-blinded study. Ideally, the investigator measuring the IOP should have been separate to the person administering the intravitreal bevacizumab as well as be blinded to the study arms. We do, however, believe that the IOP difference between the two groups was large enough that this bias would not have necessarily affected the outcome of the study. The follow-up is also for a short period of time (one intravitreal injection), and a longer follow-up with repeated injections would better assess the safety of repeated uses of the Honan balloon. Central corneal thickness (CCT) was also not measured and since it does influence IOP measurements, this is a limitation as it remains unknown whether the two groups were balanced in terms of their mean CCT. Future studies are also needed to compare the Honan balloon to other treatment modalities used to lower IOP both pre- and post-injection so that the safest, most efficacious treatment can be established.

Conclusion

Use of the Honan balloon significantly reduced the median IOP rise at 5-, 10- and 30-minutes post injection of intravitreal bevacizumab. With the above findings we recommend using the Honan balloon to reduce IOP prior to performing intravitreal anti-VEGF injections.

Ethics statement

Approval was obtained from the University of Pretoria Research Ethics Committee and was conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from the patients.

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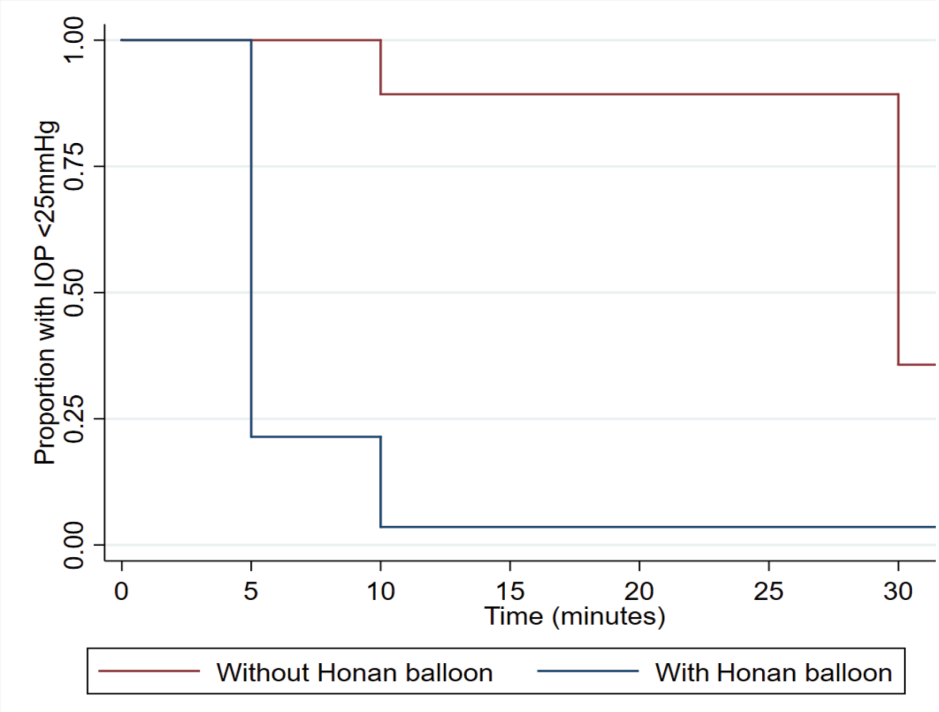

Figure 2. Kaplan-Meier curve showing the proportions of patients with IOP<25 mmHg in both study groups (p<0.001)*

**Log-rank test for equality of survivor functions*

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