ORIGINAL ARTICLE

MEAN IOP CHANGE IN NON-GLAUCOMATOUS PATIENTS WITH MACULAR EDEMA SUBSEQUENTLY INTRAVITREAL INJECTION AVASTIN

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Background: The accumulation of fluid between the retinal layers is called retinal or macular oedema, while intraretinal oedema, or macular oedema, refers to fluid accumulation directly within the retina. The purpose of the study was to evaluate the effects of intravitreal injections of bevacizumab on intraocular pressure (IOP) in Non-Glaucomatous patients with Macular Oedema. **Methods:** A pre-and post-interventional study was conducted. 220 patients were studied utilizing a non-probability, consecutive sampling method. Open Epi software was used to determine the sample size. The Department of Ophthalmology at Islamabad's Tertiary Care Hospital hosted the study, which lasted six months. **Results:** The study's participants ranged in age from 30 to 60, with a mean age of 50.38±6.53 years. Male to female ratio of these 220 patients was 1:1.6, with 86 (39.09%) men and 134 (60.91%) women. The mean IOP at baseline was 11.57±1.42 mmHg, and the mean IOP one month after the injection was 12.81±1.18 mmHg, with a mean change in IOP of 1.24±0.87 mmHg. **Conclusion:** This study found that non-glaucomatous patients with macular oedema experienced a high mean change in intraocular pressure (IOP) after intravitreal Avastin.

Keywords: Macular oedema; Intravitreal Avastin; Intraocular pressure

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INTRODUCTION

The accumulation of fluid between the retinal layers is called retinal or macular oedema, while intraretinal oedema, or macular oedema, refers to fluid accumulation directly within the retinal (e.g., sub-sensory fluid, serous retinal detachment). Osmotic and hydrostatic pressures between the retina and the surrounding vasculature maintain the normal amount of fluid in the retina, which is separated from the blood by the blood-retinal barrier. When the blood-retinal barrier is compromised, fluid can collect in the cystoid spaces found within the retina. CME may be caused, in part, by pathological evidence of cell loss and abnormalities in Müller cells[1]. A number of hypothesized mechanisms contribute to the growth of CME. Mediators (e.g. prostaglandins) released in the eye may diffuse to explain the pattern of vascular leakage and retinal oedema. It was reported in 2013 that a phakic patient with type 1 idiopathic macular telangiectasia had CME that responded strongly to NSAID treatment but would re-emerge if the patient wasn't given it.[1]

Neovascularization or macular oedema are symptoms of a number of posterior segment illnesses, and the intravitreal injection of anti-VEGF has completely changed how these ailments are managed. Some of the anti-VEGF drugs include ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA), bevacizumab (Avastin; Genentech, Inc.), pegaptanib (Macugen; Bausch & Lomb Inc., Rochester, NY), and aflibercept (Eylea; Regeneron, Tarrytown, NY).[2] They have a strong safety record and have aided many patients with conditions like diabetic macular oedema, neovascular age-related macular degeneration, and myopic choroidal neovascularization that result in retinal or choroidal neovascularization.[3,4] The FDA has authorized the systemic treatment of the monoclonal antibody bevacizumab (Avastin), which inhibits vascular endothelial growth factor (VEGF), in patients with metastatic colon cancer. Age-related macular degeneration (ARMD)-related choroidal neovascularization (CNV) was the first ocular condition for which intravitreal bevacizumab was reported in 2005. Increased intraocular pressure (IOP) is a potential side effect that may be either temporary or long-lasting.[5–7]

Most patients experience increased IOP after receiving intravitreal Avastin; this is clinically significant because it can cause permanent damage to the patient's vision and necessitates close monitoring. The average change in intraocular pressure (IOP) following intravitreal Avastin administration in patients without glaucoma is the focus of this research. Since there is a huge lack of research in this area, our findings

will not only fill a gap in the local data but also contribute to the larger body of literature on the topic.

MATERIAL AND METHODS

It was a Pre & Post Interventional Study carried out in a Tertiary care Hospital in Islamabad. Consecutive sampling (non-probability) was used. A total of 220 candidates were enrolled using the open epi software with 5% CI and .03 margin of error. The study duration was six months from October 2019 to 24th April 2020. All patients with macular oedema, 30-60 years of age, both male and female genders were included. The exclusion criteria include PRP-treated patients, h/o trauma, Glaucoma suspect, Patients on Beta Blockers, using steroid eye drops, and Raised IOP above 21 mmHg.

Following approval from an official ethics committee, 220 patients who presented to the Department of Ophthalmology at KRL Hospital in Islamabad and met the inclusion criteria were selected. Step-by-step protocols in accordance with the Helsinki Declaration were used for the study. Each participant provided written informed consent. Then, the IOP (intraocular pressure) was measured. Aseptic methods were used to anaesthetize the eye locally before the administration of intravitreal injections. Topical antibiotics and 5% topical povidone—iodine solutions were used to treat the eye prior to the injection. Bevacizumab (1.25 mg/0.05 mL) was administered through Pars Plana with a 30 gauge needle intravitreally. Sterile cotton was pressed over the injection site to prevent fluid and vitreous reflux. Patients were advised to use antibiotic drops QID daily for a week. Intraocular pressure was measured after one month of injection, in all patients. All data was recorded on a standard form, including demographic information like age, gender, disease duration, baseline readings, readings one month after injection, and the mean change in intraocular pressure.

The data was loaded into the statistical program SPSS 25.0 for further examination. In this study, we used mean and standard deviation to provide data on age, duration of macular oedema, baseline IOP, IOP one month after injection, and mean change in IOP. Hypertension status was reported as a yes/no by gender and as a frequency and percentage. Post-stratification, an independent "t" test was carried out to assess the effect of IOP increase as an outcome. A *p*-value 1.05 was considered significant.

RESULTS

Participants in this study ranged in age from 30 to 60, with a mean age of 50.38 6.53 years. 168 patients (76.36%), or the majority, were between the ages of 46 and 60. The male-to-female ratio of these 220 patients was 1:1.6, with 86 (39.09%) men and 134 women. Macular oedema persisted for 5.10 2.21 weeks on average. In this study, about 75% of patients, have a mean IOP measured and documented as being between ≤12 mmHg, and >12 mmHg in 25% of cases.

The baseline IOP was 11.57mmHg with SD of ±1.42 mmHg, and the mean IOP after 1 month of injection of Avastin was 12.81mmHg ±1.18 mmHg. In non-glaucomatous individuals with macular oedema who received intravitreal Avastin, the mean change in intraocular pressure (IOP) was 1.24± 0.87SD, with a very significant *p*-value of 0.0001. The stratification of the mean change in IOP in relation to the duration of oedema was not significant having a *p*-value of .094. However, the stratification of mean change in IOP in HTN was 1.35 ±1.03SD and a *p*-value of .0001 which is highly significant.

Figure-1: Distribution of patients according to Gender (n=220)

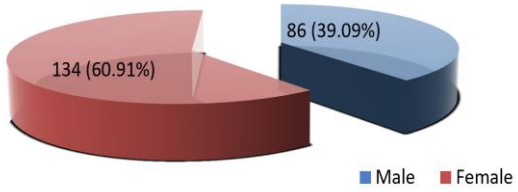

Table-1: Stratification of Mean change in IOP with respect to baseline IOP

Baseline IOP (mmHg)	change in IOP		*p*-value
	Mean	SD	
≤12	1.55	0.79	**0.0001**
>12	0.33	0.47	

Table-2: Stratification of Mean change in IOP with respect to HTN

HTN	change in IOP		*p*-value
	Mean	SD	
Yes	1.35	1.03	**0.0001**
No	1.19	0.83	

Table-3: Mean change in intraocular pressure (IOP) subsequent to Injection of Avastin in patients without Glaucomatous changes and Macular oedema

IOP (mmHg)	Mean±SD	*p*-value
Baseline	11.57±1.42	**0.0001**
Post-injection	12.81±1.18	
Change	1.24±0.87	

DISCUSSION

A minority of eyes in this prospective trial of patients treated with intravitreal anti-VEGF drugs experienced prolonged elevations in intraocular pressure (IOP).[14] In our study we find that intravitreal treatment, in which fluid is injected into the vitreous cavity to treat a variety of eye conditions, has the potential to increase IOP immediately (IOP). After receiving intravitreal anti-VEGF treatment, numerous

authors have seen a temporary (30-minute) increase in intraocular pressure (IOP).[8] Literature showed that there have been reports of brief increases in intraocular pressure (IOP) shortly after intravitreal ranibizumab or Bevacizumab administration[12,13] because an increase in vitreous volume modifies aqueous outflow. We don't know much about the mechanisms that could lead to prolonged intraocular pressure (IOP) increase following injection of Avastin.[15] A study conducted in Korea at the Eulji Medical Center to assess the effect of intravitreal antiVEGF injection on intraocular pressure (IOP) during periods: (after 30 minutes, a day, and a week after the injection), Jong Lee *et al*. discovered an increase in the IOP values immediately after the injection, which was (16.663.50) mmHg before the injection and an increased significantly after the injection to (43.819.69) mmHg and then This contradicts the findings of our investigation.[23] It is possible that anti-VEGF drugs cause direct harm to the trabecular meshwork.[16] Trabecular meshwork cells were not shown to be harmful in the literature using human cells culture treated with Avastin.[14] In 2005, choroid neovascularization (CNV) from age-related macular degeneration was reported as the first ocular condition for which intravitreal Bevacizumab was used.[9] The elevation of intraocular pressure (IOP) is a potential adverse impact that may be either temporary or long-lasting. This research was conducted to measure the average change in intraocular pressure (IOP) in non-glaucomatous patients with macular oedema following intravitreal Avastin treatment. The average intraocular pressure (IOP) at the start of our trial was 11.57mmHg ±1.42 mmHg SD, after 1 month of injection, it was 12.81mmHg with a SD of ±1.18 mmHg. The mean change was observed at 1.24 mmHg with a SD of ±0.87. A similar study published internationally showed a mean intraocular pressure (IOP) before therapy of about 13.7mmHg with a SD of ±2.8. It had been observed that the mean IOP after therapy at 1 month was 14.0mmHg with ±2.3SD with a mean change in IOP of 0.37 mmHg ± 0.28SD.[10] Extreme Intra Ocular Pressure increase probably be occur in most patients, Hollands *et al.* analyzed the change in IOP from 2–5 and repeated it after 30 minutes of 0.05 ml of Inj Avastin.[8] A study by Lemos-Ries *et al.* published in 2014 confirmed that IOP rises after intravitreal injection of bevacizumab, with some patients experiencing readings of 50 mmHg or higher.[9] Yogish *et al*, an Indian study to investigate the changes in IOP after intravitreal Avastin injection, found an increase in IOP values at 4 hours compared to pre-injection and found no significant increase in values after 2 and 6 weeks of injection compared to pre-injection. This is in contrast to our findings.[21] If no subconjunctival reflux occurs, then intraocular pressure (IOP) should be greater, as shown by a 2016 study by Lee *et al*., who also found that an immediate rise in IOP caused by intravitreal anti-VEGF injection was associated with a temporary drop in mean ocular perfusion pressure.[11] Another study published recently showed that the mean increase after 1 month of intravitreal injection was observed 0.278 with a SD of 2.55mmHg and a *p*-value of <.0001.[12] Several studies have examined at increases in intraocular pressure (IOP) after injection, and they have all concluded that these increases are temporary and that anterior chamber paracentesis, another method of reducing IOP, is unnecessary.[11,17,18] After 6 months of intravitreal bevacizumab injection, Sulman Jaffar *et al*. found a statistically significant rise in IOP average values compared to its value before injection. According to our findings, this is true; nonetheless, the mean IOP value did not rise at all after a year.[24]

The baseline IOP recorded prior to each injection was compared to the IOP at subsequent visits in order to check the effect of inj Avastin on IOP change. Table 1 shows that individuals with a baseline IOP of ≤12 mmHg had a greater average IOP change than those with a baseline IOP of >12 mmHg. With a *p*-value of .0001, the *p*-value was very significant. Mansoori T *et al.* recently reported a study that found an increase in IOP after anti-VEGF medication compared to baseline IOP measurements, and it was highly significant after 1 month of follow-up. The mean difference in IOP was found to be 0.278 with a *p*-value of 0.0001[12]. The paper further explains that the IOP difference was greater in those with a higher baseline IOP, which is contradictory to our findings. A subsequent study indicated that there was only a small rise in IOP compared to baseline readings and that it returned to normal after 30 minutes, making it safe.[11] But in our study, we saw a noticeable change even one month after the injection, and in some cases, up to a year later.

In our research, we found that people with HTN had significantly higher intraocular pressure (IOP) than those without the condition mentioned in Table 2. Previous research by Rasier *et al.* found a rise in blood pressure after intravitreal Avastin injection when monitored at 1, 3, and 6 weeks.[19] Systemic hypertension, which can be thought of as a systemic problem following intravitreal Avastin injection, was also flagged as a potential adverse effect by Rasier *et al*.[19] However other research indicated that higher BP was not associated with Intravitreal injection rather than the patient will be hypertensive before to the injection but undetected. In our study, Table 3 revealed that individuals with Macular Oedema but non-glaucomatous had an increase in IOP postoperatively with a strong statistical significance and a *p*-value of <.0001. Previous research mostly enrolled patients with

AMD, with only a few trials involving individuals with DME.[20] In a study conducted in Chicago, and similar to ours, IOP was measured during the months (0–6, 6–12, 12–18, 18–24, and > 24) after the injection of antiVEGF and compared the results with the values of IOP before injection, and they measured no significant increase in IOP post injection during the follow-up period, which is inconsistent with our study.[21,26]

Strength & Limitation of the Study: The prospective design of the current study is both its strength and power. Short follow-up time, absence of a control group, and inconsistent injection technique are some of the downsides.

CONCLUSION

This study found that the average change in IOP following intravitreal Avastin was fairly substantial in patients without glaucoma who had macular oedema. Since advanced visual functional deficits can be avoided if IOP elevation is treated early and effectively, we advise that this approach be used with these patients.

AUTHORS' CONTRIBUTION

AA: Basic concept, data collection, literature Review. AHA: Supervision and literature search. AI: Proof reading. SAK: Write-up, literature search. MS: Conceptualization of study design, data analysis. MN: Data Interpretation.

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