

Is perioperative blood pressure monitoring during intravitreal injections important?

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Abstract

Background: Anti-vascular endothelial growth factor intravitreal injections (IVIs) have proved to be a boon for patients suffering from several retinal pathologies. They are one of the most commonly performed procedures in ophthalmology. A perioperative rise in blood pressure (BP) has been noted during cataract surgery.

Objectives: To evaluate the perioperative BP changes during IVI, and the associated risk factors.

Design: Cross-sectional observational study

Methods: The patients undergoing IVI from May 2019 to August 2019 were evaluated. All the patients underwent BP measurement before, during, and 1 h after the IVI. The correlation between the demographics and, the systemic comorbidities of the patients, and the ocular condition for which IVI was given was evaluated.

Results: The study included 302 patients (mean age of 59.9 ± 10.7 years). The mean increase in systolic BP (SBP) and diastolic BP (DBP) at the time of injection was 25.7 ± 21.0 and 1.3 ± 13.4 mmHg, respectively. A ≥ 10 , ≥ 20 , ≥ 30 mmHg increase in SBP at the time of injection was seen in 83.8% ($n = 253$), 69.5% ($n = 210$) and 49.0% ($n = 148$) patients, respectively. Forty-one (13.6%) patients developed intra-procedural hypertensive urgency, out of which six patients (14.6%) did not recover even after 1 h of the procedure. None of the patients experienced any cardiovascular events. The univariate and multivariate linear regression analyses showed that the change in intra-procedural SBP correlated positively with the age of the patient and negatively with the baseline SBP.

Conclusion: There is a significant rise of SBP at the time of IVI, especially in patients with advanced age and high baseline SBP. Some of the patients can experience hypertensive urgency at the time of injection and may take more than 1 h to recover. The patients receiving IVI should undergo a detailed physician evaluation before the procedure.

Keywords: anti-vascular endothelial growth factor (VEGF), blood pressure, intravitreal injections (IVIs), perioperative anxiety

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Introduction

Anti-vascular endothelial growth factor (VEGF) intravitreal injections (IVIs) have proved to be a boon for patients suffering from several retinal pathologies such as diabetic macular edema, age-related macular degeneration, retinal venous occlusion. They are one of the most commonly performed procedures in the field of ophthalmology. Unlike other surgical procedures, anti-VEGF

injections have to be repeated multiple times due to their small half-life.^{1–3}

A perioperative rise in blood pressure (BP) has been noted during cataract surgery.^{4–8} In fact, the guidelines from the American Academy of Ophthalmology suggest that BP monitoring should be performed during cataract surgery by personnel, other than the operating ophthalmologist, who is

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qualified to monitor and manage the patient's systemic status.^{9,10} In addition to the intraoperative BP rise, intravitreal anti-VEGF injections have been demonstrated to increase the lifelong risk of cardiovascular and cerebrovascular events.¹¹

This study aims to evaluate the perioperative change in BP during IVI and associated risk factors.

Materials and methods

This observational, cross-sectional study was conducted at a tertiary-care eye hospital in South India with approval from the Institutional Review Board (Aravind Medical Research Foundation, Registration No. ECR/182/INST/TN/2013, dated 20 April 2013). The study protocol adhered to the tenets of the Declaration of Helsinki. Written informed consent for inclusion into the study was taken from each patient apart from the regular consent for IVI.

All the patients who underwent IVI of bevacizumab from May 2019 to August 2019 were included in the study. A manual clock-type non-mercuric sphygmomanometer was used to measure BP (Diamond BPDFL 237 clock-type BP monitor; Diamond Industrial Electronic and Allied Products, Pune, India). The measurements were repeated by the same person using the same instrument each time.

All the patients received the injections under topical anaesthesia inside a sterile operating room (OR). The patients were first examined on a slit lamp and then shifted to a waiting area, where the first BP recording (BP-1) was taken. Topical proparacaine drops (0.5%) and 5% povidone-iodine drops were applied in the conjunctival sac before the patients were shifted inside the OR. Inside the OR, the patients were made to lie down, topical proparacaine drops (0.5%) were repeated and the periorbital area was cleaned with 10% povidone-iodine. A self-adhesive sterile eye drape large enough to mask the patient's face and cover his other eye was then placed. A speculum was placed and 5% povidone-iodine drops were again applied in the conjunctival sac for 1 min. The second BP recording (BP-2) was taken during this time. The eye was then washed with sterile saline. The IVIs were injected through the pars plana 3.5–4 mm from the limbus using a 30-gauge needle. The eye drape was then removed, the eye was patched and the patient was shifted outside the OR. The third

BP recording (BP-3) was taken in the waiting room 1 h after the procedure. The patients were discharged once the BP normalized. None of the patients received simultaneous bilateral injections. In case injection was indicated in both the eyes, they were separated by at least 7–10 days. Patients who received bilateral injections were recruited in the study only during the first IVI visit. Hypertensive urgency was defined as systolic BP (SBP) >180 mmHg or diastolic BP (DBP) >120 mmHg.^{12,13}

The records were evaluated for the perioperative BP change, the incidence of hypertensive crisis and correlation with risk factors such as age, gender, systemic comorbidities, the indication of injection and the number of previous injections.

Data analysis

Statistical analysis was performed with STATA statistical software, Version 11.1 (StataCorp, College Station, TX, USA). The continuous variables were expressed as mean (\pm standard deviation) and categorical variables were expressed as percentages. The comparison between categorical data was performed with chi-square/Fisher exact test, while the difference in continuous data was measured with Student *t* test/Mann–Whitney test. One-way analysis of variance was applied to compare continuous variables in each group over time. Regression analysis was performed to find the effect of patient variables on the change in pressure measurements during the procedure. A two-tailed *p* value less than 0.05 was considered to be statistically significant.

Results

The study included 302 patients (302 eyes), who received IVI. A total of 201 males (66.6%) and 101 females (33.4%) were recruited. The average age of the patients was 59.9 ± 10.7 years. The systemic comorbidities among the patients included diabetes mellitus (DM, $n = 219$, 72.5%), hypertension (HTN, $n = 160$, 52.9%), chronic kidney disease (CKD, $n = 14$, 4.6%) and ischemic heart disease (IHD, $n = 14$, 4.6%). The indications for performing the IVI were branch retinal venous occlusion (BRVO, $n = 46$, 15.2%), central RVO ($n = 42$, 13.9%), choroidal neovascular membrane (CNVM, $n = 56$, 18.5%), nonproliferative diabetic retinopathy (NPDR, $n = 69$, 22.8%), neovascular glaucoma (NVG, $n = 10$, 3.3%), proliferative diabetic retinopathy (PDR, $n = 66$,

Table 1. Summary of various mean blood pressure measurements at various points of time.

Timing	Station 1 Before shifting to injection OR	Station 2 Inside injection OR	Station 3 Recovery room after injection
Mean SBP (mmHg)	133.6 ± 17.9	159.3 ± 24.5	144.4 ± 19.9
Mean DBP (mmHg)	78.1 ± 8.9	79.4 ± 12.7	82.5 ± 10.3
Mean MAP (mmHg)	96.7 ± 10.6	106 ± 13.5	103.1 ± 13.5

DBP, diastolic blood pressure; MAP, mean arterial pressure; OR, operating room; SBP, systolic blood pressure.

21.8%) and polypoidal choroidal vasculopathy (PCV, $n = 13$, 4.3%).

The mean SBP-1, SBP-2 and SBP-3 were 133.6 ± 17.9 , 159.3 ± 24.5 and 144.4 ± 19.9 mmHg, respectively ($p < 0.001$). The mean DBP-1, DBP-2 and DBP-3 were 78.1 ± 8.9 , 79.4 ± 12.7 and 82.5 ± 10.3 mmHg, respectively ($p < 0.001$). The mean arterial pressure 1, 2 and 3 were, respectively, 96.7 ± 10.6 , 106 ± 13.5 and 103.1 ± 13.5 mmHg (Table 1). At the time of injection, the mean increase in SBP (SBP2-SBP1), DBP (DBP2-DBP1) and MAP (MAP2-MAP1) were 25.7 ± 21.0 , 1.3 ± 13.4 and 9.4 ± 13.6 mmHg, respectively. While the intra-operative SBP was significantly higher than the baseline value ($p < 0.001$), intraoperative DBP was similar to baseline ($p = 0.207$). At the time of procedure, SBP increase of ≥ 10 , ≥ 20 , ≥ 30 mmHg was seen in 83.8% ($n = 253$), 69.5% ($n = 210$) and 49.0% ($n = 148$) patients.

None of the patients had baseline SBP > 180 mmHg. A total of 41 patients (13.6%) developed hypertensive urgency at the time of IVI, out of which 6 (1.9%) did not recover even after 1 h of the procedure and received necessary treatment. None of the patients had DBP > 120 mmHg at any point. None of the patients developed any cardiovascular events during their hospital stay.

Using logistic regression analysis, we found that the presence of hypertensive crisis at the time of injection was not associated with age, gender, number of previous injections, indication for injection and presence of systemic comorbidities. Univariate linear regression analysis showed that the change in intra-procedural SBP (SBP2-SBP1) correlated positively with the age of the patient [$R = 0.25$, 95% confidence interval (CI): 0.02 to 0.47, $p = 0.029$] and negatively with baseline SBP ($R = 0.25$, 95% CI: 0.38 to -0.12 , $p < 0.001$). Multivariate linear regression analysis showed that

the change in intra-procedural SBP correlated positively with the age of the patient ($R = 0.33$, 95% CI: 0.11 to 0.55, $p = 0.004$) and negatively with baseline SBP ($R = 0.28$, 95% CI: 0.42 to -0.15 , $p < 0.001$). Univariate and multivariate linear analyses showed that the presence of systemic diseases, intake of antihypertensive medications and the ocular condition for which the IVI was given did not correlate with the mean intra-procedural change of SBP (Table 2).

Discussion

Hypertensive crisis is defined as SBP > 180 mmHg or DBP > 120 mmHg. Such patients are at a high risk of end-organ damage. The condition is termed 'hypertensive emergency' in the presence of associated organ damage, such as stroke or myocardial infarction. These patients need immediate BP control in an intensive care setting to prevent further organ damage, that is, around 25% lowering in the first 1–2 h. The condition is termed as 'hypertensive urgency' in the absence of end-organ damage. Such patients can be treated in an outpatient setting as BP can be controlled slowly in 24–48 h.^{12,13} Any intra-procedural hypertensive emergency can prove catastrophic, especially in ophthalmic hospitals, which usually lack an extensive intensive care setup.

Apart from the various systemic complications, accelerated HTN can also lead to hypertensive retinopathy. Sudden rise in BP can lead to malignant HTN, which presents with cotton wool spots, retinal hemorrhages, focal intraretinal periarteriolar transudates, disc edema, macular edema, macular hard exudates, Elschnig's spots, Siegrist's streak and serous retinal detachment.^{14,15} Vision loss may occur due to retinal pigmentary changes secondary to exudative retinal detachment and optic atrophy secondary to papilloedema. It also increases the risk of other vision-threatening pathologies such as branch retinal artery occlusion (BRAO), central RAO,

Table 2. Factors associated with mean intra-procedural change of systolic blood pressure using linear regression analysis.

	Univariate analysis		Multivariable analysis	
	Co-efficient (95% CI)	<i>p</i> value	Co-efficient (95% CI)	<i>p</i> value
Age	0.25 (0.02 to 0.47)	<i>0.029</i>	0.33 (0.11 to 0.55)	<i>0.004</i>
Gender	-2.57 (-7.60 to 2.46)	0.316	-2.74 (-7.67 to 2.19)	0.274
Number of previous injections	-0.27 (-1.0 to 0.45)	0.457	-0.63 (-1.35 to 0.09)	0.085
Systemic diagnosis				
Diabetes mellitus	0.34 (-4.98 to 5.67)	0.899	1.56 (-3.72 to 6.85)	0.561
Hypertension	-0.83 (-5.59 to 3.94)	0.733	0.71 (-4.15 to 5.58)	0.773
CKD	-5.97 (-17.27 to 5.32)	0.299	-3.07 (-14.37 to 8.22)	0.593
Baseline SBP	-0.25 (-0.38 to -0.12)	<i><0.001</i>	-0.28 (-0.42 to -0.15)	<i><0.001</i>
Ocular diagnosis				
BRVO	0.36 (-6.3 to 7.0)	0.915	8.77 (-4.2 to 21.8)	0.185
CNVM	-0.04 (-6.2 to 6.1)	0.989	8.43 (-4.3 to 21.2)	0.194
CRVO	-2.19 (-9.1 to 4.7)	0.531	6.58 (-6.6 to 19.7)	0.325
NPDR	3.78 (-1.9 to 9.4)	0.189	11.38 (-1.1 to 23.9)	0.075
NVG	4.25 (-9.0 to 17.5)	0.530	12.57 (-4.8 to 30.0)	0.156
PCV	-8.85 (-20.5 to 2.8)	0.137	-	-
PDR	-1.26 (-7.0 to 4.5)	0.667	-7.48 (-5.1 to 20.0)	0.242
BRVO, branch retinal vein occlusion; CI, confidence interval; CKD, chronic kidney disease; CNVM, choroidal neovascular membrane; CRVO, central retinal vein occlusion; NPDR, nonproliferative diabetic retinopathy; NVG, neovascular glaucoma; PCV, polypoidal choroidal vasculopathy; PDR, proliferative diabetic retinopathy; SBP, systolic blood pressure. The significant values have been written in italics.				

BRVO, CRVO, retinal artery macroaneurysm, nonarteritic anterior ischemic optic neuropathy and progression of diabetic retinopathy.¹⁶

We found that there was a significant rise in absolute SBP at the time of injection. Previously, Berger *et al.*¹⁷ have demonstrated that SBP may

rise by 18 ± 15 mmHg at the time of IVI. Wyssmüller *et al.*¹⁸ also found that SBP rose from 157.3 ± 5.9 mmHg to 175 ± 6.7 mmHg at the time of the injection. Our study found that an SBP rise of ≥ 10 and ≥ 20 mmHg was seen in 83.8% and 69.5% of patients. This was comparatively higher than reported by Berger *et al.*,¹⁷ who

reported an incidence of 72% and 46%, respectively. We also found that nearly 14% of patients had hypertensive urgency at the time of injection, out of which nearly 15% (overall around 2% of study patients) did not recover even after 1 h. Similarly, Berger *et al.*¹⁷ reported that 11% of patients had SBP > 200 mmHg at the time of injection. However, there were no cardiovascular events documented in either of the studies.¹⁷

We did not find any association between the occurrence of hypertensive crisis at the time of injection with any of the study variables. However, advanced age and higher baseline SBP were found to be associated with a higher rise of SBP during the injection. Similarly, Berger *et al.*¹⁷ found age to be associated with an SBP > 200 mmHg during the injection. Balci *et al.*¹⁹ reported that intra-procedural rise in SBP was higher in hypertensive patients compared with normotensive ones. However, we could not find such an association.

The rise in SBP at the time of injection may be a result of anxiety or alertness especially due to the use of an eye drape that covers the other eye also. This may be similar to the well-known 'white coat hypertension', caused by the patient's nervousness at the conscious or subconscious level.^{20,21} Berger *et al.*¹⁷ also found no association between the intra-procedural BP rise and the anxiety levels; however, discomfort after the previous injection correlated with intra-procedural BP rise. Another cause of the rise in SBP could be the irritation caused by the use of topical povidone-iodine drops. However, the use of these drops cannot be avoided as these drops have been shown to be indispensable in reducing the incidence of endophthalmitis following an intraocular procedure.^{22,23}

In our study, the patients were injected in an OR along with the use of a face-covering drape as well as eye speculum. However, IVIs are performed as an office procedure at some centres. Techniques which avoid the use of eye speculum like bimanual-assisted eyelid retraction and lid splinting eyelid retraction techniques have also been described.^{24,25} However, there are no studies which have evaluated the changes in intra-procedural BP using these techniques.

Limitations of the study include the use of a single anti-VEGF agent and a single injecting technique. Also, single unblinded investigator performed all the BP measurements manually and could have been a potential source of bias. The results of this

study show that there is a significant rise of SBP at the time of IVI, especially those with advanced age. Several patients go can into hypertensive urgency during the procedure and some may not recover even after 1 h, requiring additional treatment. The procedure may be short but is not as innocuous as is thought to be. The patients undergoing IVI should have a pre-operative evaluation and undergo the procedure only after an adequate BP control. The physicians must be careful while evaluating the patients with systemic comorbidities due to higher risk of cardiovascular and cerebrovascular events is higher.

Author contributions

Meri Debbarma: Conceptualization; Data curation; Funding acquisition; Resources; Writing – review & editing.

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Conflict of interest statement

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