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ORIGINAL ARTICLE

Temporal fluctuations of cardiovascular parameters after intravitreal injections

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Abstract

Background: Despite the effectiveness of intravitreal injection (IVI) of anti–vascular endothelial growth factor in treating retinal diseases, there remains a paucity of evidence on potential systemic risks associated with this procedure. This study aims to investigate cardiovascular parameters and the risk of hypertensive urgency after IVIs.

Methods: Patients who received IVIs for retinal/macular diseases were enrolled retrospectively. Patients who received cataract surgeries were enrolled as controls. Systolic and diastolic blood pressure (BP) and heart rate were measured 10 minutes before, immediately after, and more than 30 minutes after IVIs and cataract surgery. Multivariate analysis was performed to evaluate risk factors for hypertensive urgency.

Results: Seventy patients who received IVIs and 95 patients who received cataract surgeries were enrolled. A higher preoperative systolic BP was found in the IVI groups than in the control group (147.0 ± 22.9 vs 136.3 ± 21.8 mmHg, respectively). The patients who received IVIs had a higher increase in perioperative systolic BP immediately after the procedure than the controls (17.43 ± 20.53 mmHg vs 9.11 ± 18.92 mmHg, $p = 0.009$). The IVI procedure (odds ratio [OR] 4.84, $p = 0.008$), preoperative systolic BP ≥160 mmHg (OR 17.891, $p = 0.001$, compared to preoperative systolic BP <140 mmHg), and underlying hypertension (OR 3.305, $p = 0.041$) were risk factors for hypertensive urgency immediately after the IVIs.

Conclusion: We found a transient increase in BP after IVIs, which may have been associated with hypertensive urgency and related cardiovascular disorders in older patients and in those with relevant comorbidities. Clinicians should pay more attention to these patients before performing IVIs.

Keywords: Hypertensive urgency; Intravitreal injection; Risk factor; Temporal cardiovascular parameter

1. INTRODUCTION

Intravitreal injections (IVIs) have become one of the most common intraocular procedures for many retinal diseases. IVIs of anti–vascular endothelial growth factor (anti-VEGF) agents including bevacizumab, aflibercept, and ranibizumab are widely used for neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), retinal vein occlusion (RVO), and myopic choroidal neovascularization (mCNV).[1–4] Intraocular steroids including triamcinolone and dexamethasone implants have also been used for macular edema secondary to DME and RVO.[5]

Systemic anti-VEGF treatment, which inhibits the VEGF signaling pathway, has been reported to potentially cause side effects of hypertension, cardiac thrombosis, myocardial infarction, and cerebrovascular disease.[6,7] In contrast, clinical studies and meta-analyses have shown no significant increase in vascular adverse effects or mortality in patients treated with anti-VEGF IVIs.[7,8] However, potential risks of the IVI procedure itself have rarely been discussed. The procedure may induce stress or anxiety, which would activate the autonomic nervous system and hypothalamic pituitary adrenal axis.[9] These stress responses are accompanied by elevated heart rate (HR) and blood pressure (BP) and the release of stress hormones. These responses can also increase the workload of the heart, and dysregulation of the autonomic nervous systems can lead to cardiovascular diseases.[10–12]

Therefore, it is important to evaluate whether there are any potential risks of the IVI procedure itself, such as perioperative changes in cardiovascular parameters. In this study, we retrospectively evaluated changes in BP before and after IVIs, and compared the results with a control group of patients who underwent cataract surgeries. The aim of this study was to investigate whether there was a transient increase in BP during the IVI procedure and to evaluate risk factors for cardiovascular or cerebrovascular effects.

2. METHODS

2.1. Participants

This retrospective observational study was conducted at a single tertiary referral center (Department of Ophthalmology, Taipei Veterans General Hospital, Taipei, Taiwan). The study

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was conducted according to the Declaration of Helsinki and approved by the Institutional Review Board for Human Research of Taipei Veterans General Hospital (2021-02-004CC). We carefully reviewed the medical records of patients who received an IVI or cataract surgery between January 2019 and April 2019 by two senior ophthalmologists (D.-K. Hwang and Y.-B. Chou). All the procedures were performed by the original physicians in person and in the same operation setting. We included patients who underwent IVI or cataract surgeries under topical anesthesia and included patients whose systolic BP (SBP), diastolic BP (DBP), and HR were recorded in the medical charts. IVI agent administration and demographic data, such as the incidence of hypertension, diabetes, use of anticoagulants, and chronic kidney disease, were reviewed carefully. Patients who underwent cataract surgeries combined with IVI, surgeries under the application of retrobulbar anesthesia, or surgeries under general anesthesia were excluded.

2.2. Procedure of IVIs and cataract surgeries

All the surgeries were performed in a sterile operating room. IVI surgeries and cataract surgeries were performed after the application of topical anesthesia. After sterilizing with 5% povidine-iodine and with an eyelid speculum, sterile calipers were used to mark the insertion site: 3.5 mm for pseudophakes and 4 mm for phakes. A thirty-gauge needle was inserted perpendicular to the vitreous to deliver medications, including aflibercept (2 mg/0.05 mL of Eylea; Bayer Healthcare, Leverkusen, Germany), ranibizumab (0.5 mg/0.05 mL of Lucentis; Genentech, Inc.; South San Francisco, CA, USA), dexamethasone intravitreal implant (0.7 mg of Ozurdex; Allergan, Inc., Irvine, CA, USA), and methotrexate (200 μg/0.05 mL; Hospira, Inc., Lake Forest, IL, USA) in one eye. After the same sterile steps, cataract surgeries were performed with phacoemulsification and posterior capsular intraocular lens insertion.

2.3. Measurement of BP and HR

As recorded, after patients arrived at the operating room, they were asked to rest for 10 minutes. BP and HR were self-measured using an automated sphygmomanometer (BPBIO320; InBody Co., Ltd, Seoul, South Korea) 10 minutes before (T0) and immediately after the procedure (T1) under sitting position. Postoperative BP and HR were recorded >30 minutes after the procedure (T2). Much high or low BP/HR data were checked repeatedly. BP/HR monitors fulfilled the protocol of the Association for the Advancement of Medical Instrumentation.[13]

2.4. Statistical analysis

Statistical analyses were performed using SPSS software (version 24; SPSS, Inc., Chicago, IL, USA). If the patients received the repeated procedure more than once during the study period (e.g., cataract surgeries for bilateral cataracts or repeated IVIs for recurrent maculopathy), only one of the BP and HR results was randomly included in the analysis. Changes in BP and HR at T0, T1, and T2 were analyzed using the paired *t* test. BP, HR, age, and the incidence of hypertension, diabetes, use of anticoagulants, and chronic kidney disease were compared between the patients who received IVIs and those who received cataract surgery (the control group) using the independent *t* test and chi-square test. The cutoff postoperative BP values were SBP ≥180 mmHg and DBP ≥110 mmHg based on the definition of hypertensive urgency according to the Eighth Joint National Committee guidelines (JNC 8).[14] The cutoff value of preoperative SBP was categorized as <140, ≤140–160, and ≥160 mmHg based on the classification of hypertension on office BP. To test multicollinearity, we used collinearity diagnostics to test tolerance and variance inflation factor (VIF). Tolerance <0.1 and VIF > 10 were considered as collinearity. Univariate logistic regression analysis was used to identify factors potentially associated with a change in BP. Factors with a p value of ≤0.1 in the univariate analysis and without collinearity were included in the multivariate regression analysis. Statistical significance was set at $p \leq 0.05$.

3. RESULTS

3.1. Participants

One hundred thirty-one eyes receiving IVIs and 129 eyes as the control were enrolled in this study. A total of 47 patients received IVIs twice and 7 patients received IVIs three times. Among these patients, the first completely recorded data were chosen for analysis. Finally, 70 eyes in 70 patients were included. The medications used in the IVIs included aflibercept in 49 eyes, ranibizumab in 18 eyes, dexamethasone intravitreal implant in 2 eyes, and methotrexate in 1 eye. A total of 34 eyes in the control group were excluded, including those of patients undergoing retrobulbar anesthesia (n = 32) and concurrent IVI and phacoemulsification (n = 2), and no patient received bilateral cataract surgeries. The demographic data including age, gender, hypertension, diabetes, use of anticoagulants, and chronic kidney disease are listed in Table 1.

3.2. BP and HR after the procedure and related cardiovascular disorders

In the IVI group, the SBP was 146.99 ± 22.85 mmHg, 164.41 ± 22.98 mmHg, and 140.56 ± 22.16 mmHg at T0, T1, and T2, respectively. The DBP was 72.07 ± 15.36 mmHg, 80.17 ± 15.05 mmHg, and 69.44 ± 15.70 mmHg at T0, T1, and T2, respectively. The HR was 78.94 ± 13.12 bpm, 77.07 ± 13.41 bpm, and 78.81 ± 11.24 bpm at T0, T1, and T2, respectively. Paired *t* test analysis (Fig. 1) revealed significantly higher SBP and DBP at T1 compared with T0 and T2 in both the IVI and control groups. However, the change in HR was not significant in the IVI group.

Compared with the control group (Table 1), the patients in the IVI group had higher preoperative SBP and DBP and a greater increase in perioperative SBP (SBP (T1–T0) = 17.43 ± 20.53 mmHg, p = 0.009; SBP (T1–T2) = 23.86 ± 21.22 mmHg, p < 0.001). The patients who received IVI were older (mean age 72 vs 68 years, p = 0.022) and had a higher rate of diabetes (47.1% vs 22.1%, p = 0.001). There were no significant differences in gender, hypertension, use of anticoagulants, or chronic renal disease between the two groups.

3.3. Risk factors for hypertensive urgency

In the subgroup analysis of patients with hypertensive urgency (Table 2), IVI, higher preoperative SBP, systemic history of hypertension, and diabetes were associated with a higher increase in SBP in the univariate logistic regression analysis. Collinearity diagnosis revealed no collinear relation with preoperative SBP, hypertension and diabetes. Multivariate logistic regression analysis revealed that IVI (odds ratio [OR] 4.840, p = 0.008), hypertension (OR 3.305, p = 0.041), and higher preoperative SBP were significantly associated with a higher perioperative SBP. Compared with patients with preoperative SBP <140 mmHg, subjects with preoperative SBP 140–160 mmHg (OR 7.966, p = 0.013) and ≥160 mmHg (OR 17.891, p = 0.001) were at risk of hypertensive urgency. In the patients who received IVIs (n = 70), there were no significant differences in the risk of hypertensive urgency between the different anti-VEGF medications (OR 1.859, p = 0.334 and OR 0.522, p = 0.497 with perioperative SBP ≥180 mmHg and DBP ≥110 mmHg, respectively; Table 3).

Table 1

Demographics, blood pressure, and heart rate difference between the IVI and the phacoemulsification group

	IVI (n = 70)	Phaco (n = 95)	*p*
Median, age, y (range)	72 (46–96)	68 (42–93)	0.022*
Male (%)	43 (61.4)	49 (51.6)	0.112
Hypertension (%)	36 (51.4)	34 (35.8)	0.083
Diabetes (%)	33 (47.1)	21 (22.1)	0.001*
Anticoagulants (%)	15 (21.4)	10 (10.5)	0.238
Chronic kidney disease (%)	17 (24.3)	8 (8.4)	0.063
SBP (T1–T0), mmHg	17.43 ± 20.53	9.11 ± 18.92	0.009*
SBP (T1–T2), mmHg	23.86 ± 21.22	8.01 ± 21.92	<0.001*
DBP (T1–T0), mmHg	8.10 ± 14.45	6.00 ± 12.38	0.286
DBP (T1–T2), mmHg	10.73 ± 15.72	12.14 ± 13.40	0.547
MAP (T1–T0), mmHg	11.21 ± 13.43	7.04 ± 13.05	0.048*
MAP (T1–T2), mmHg	15.10 ± 15.28	10.76 ± 14.59	0.069
HR (T1–T0), bpm	–1.87 ± 10.91	–4.63 ± 11.43	0.123
HR (T1–T2), bpm	–2.11 ± 12.97	–3.30 ± 14.42	0.594

Time 0 (T0) indicated 10 minutes before intravitreal injection or phacoemulsification.
Time 1 (T1) occurred immediately after surgical procedure.
Time 2 (T2) indicated time after the surgeries more than 30 minutes.
DBP = diastolic blood pressure; HR = heart rate; IVI = intravitreal injection; MAP = mean arterial pressure; Phaco = phacoemulsification under topical anesthesia; SBP = systolic blood pressure.
*Statistical significance was set at $p \leq 0.05$ compared between IVI and cataract surgery.

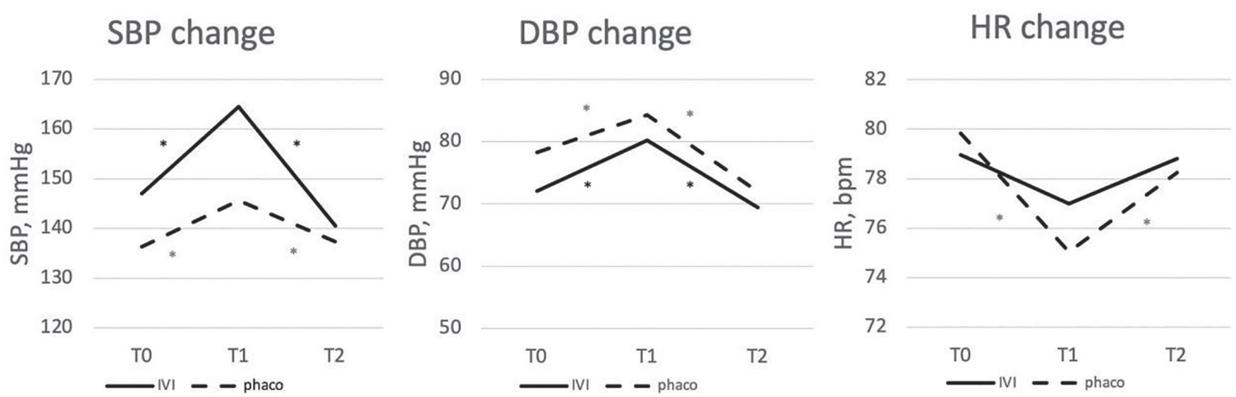

Fig. 1 Blood pressure and heart rate change in the intravitreal injection (IVI) and the phacoemulsification group. *Statistical significance was set at $p \leq 0.05$ compared between IVI and cataract surgery. Time 0 (T0) indicated 10 min before intravitreal injection or phacoemulsification. Time 1 (T1) occurred immediately after surgical procedure. Time 2 (T2) indicated time after the surgeries more than 30 min. DBP = diastolic blood pressure; HR = heart rate; IVI = intravitreal injection; SBP = systolic blood pressure; topical phaco = phacoemulsification under topical anesthesia.

No significant risk factors were found in the subgroup analysis of patients with perioperative DBP ≥110 mmHg (Supplementary Table 1).

4. DISCUSSION

In this study, we demonstrated that both SBP and DBP were significantly increased following IVI and phacoemulsification. In the IVI group, higher preoperative SBP and underlying hypertension were related to the increased risk of hypertensive urgency, suggesting that the IVI procedure itself may have influenced some of the patients' cardiovascular parameters. There were no significant associations between the different anti-VEGF medications.

Systemic anti-VEGF treatment may cause the side effects of hypertension and cardiac thrombotic events by inhibiting the VEGF signaling pathway.[6] However, the International Intravitreal Bevacizumab Safety Survey[8] which included 7113 injections in 5228 patients revealed a systemic adverse effect rate of 0.21%. In addition, the survey reported the following low side effect rates: BP increase (0.21%), deep venous thrombosis (0.01%), transient ischemic attack (0.01%), cerebrovascular accident (0.07%), myocardial infarction (0%), and death (0.03%). Another systematic review and meta-analysis of randomized trials comprising 6596 patients with AMD identified no protective or harmful effects of ranibizumab.[15] In contrast, Berger reported that 11% of their patients (23 patients) had SBP >200 mmHg following IVIs and suggested that perioperative BP or antihypertensive medications should be considered.[16] DME patients receiving monthly IVI injections have been reported to have an increased risk of cardiovascular events compared to those receiving sham and laser therapies.[7] Because few studies have investigated BP or HR changes during the procedure or whether any risk factors are related to a transient rise in BP, it is important to evaluate changes in BP and HR following IVI and analyze cardiovascular or cerebrovascular risk factors.

Stress and anxiety could be associated with changes in BP. Berger et al reported that discomfort (stepwise forward regression, $R = 0.311$, $p = 0.02$) after the last injection was associated with a high BP during IVI.[16] A meta-analysis study of 25,786 subjects reviewed the long-term cardiovascular risk in patients with white-coat hypertension and found increased risks of

Table 2

Univariate and multivariate logistic regression in the subgroup analysis of patients with systolic BP ≥180 mmHg immediately after operation (n = 25)

	Univariate SBP ≥180 mmHg OR (*p*)	Multivariate SBP ≥180 mmHg Adjusted OR (*p*)
Age	1.025 ($p = 0.174$)	—
Male	1	
Female	1.037 ($p = 0.933$)	—
Topical phaco	1	1
IVI	7.543 ($p < 0.001$)*	4.840 ($p = 0.008$)*
Preoperative SBP[a]		
<140	1	1
≥140 to <160	8.721 ($p = 0.007$)*	7.966 ($p = 0.013$)*
≥160	27.632 ($p < 0.001$)*	17.891 ($p = 0.001$)*
Hypertension[a]	4.243 ($p = 0.004$)*	3.305 ($p = 0.041$)*
Diabetes[a]	2.482 ($p = 0.042$)*	1.031 ($p = 0.956$)
Anticoagulants	0.688 ($p = 0.538$)	—
Chronic kidney disease	2.027 ($p = 0.193$)	—
Collinearity statistics[a]	Tolerance	VIF
Preoperative SBP	0.940	1.063
Hypertension	0.910	1.099
Diabetes	0.895	1.118

[a]Tolerance <0.1 and VIF>10 was considered as collinearity.

*Statistical significance was set at $p \leq 0.1$ in the univariate analysis and $p \leq 0.05$ in the multivariate analysis.

IVI = intravitreal injection; phaco= phacoemulsification under topical anesthesia; OR = odds ratio; SBP = systolic blood pressure; VIF = variance inflation factor.

Table 3

Logistic regression in the subgroup analysis of patients with hypertensive urgency immediately after injection of different IVI agents (n = 70)

	Univariate SBP ≥180 mmHg Odds ratio (*p*)	Univariate DBP ≥110 mmHg Odds ratio (*p*)
IVI-Ranibizumab (n = 18)	1	1
IVI-Aflibercept (n = 49)	1.859 ($p = 0.334$)	0.522 ($p = 0.497$)
IVI-Dexamethasone implant (n = 2)	[a]	[a]
IVI-Methotrexate (n = 1)	[a]	[a]

[a]Analysis error due to limited data. IVI-others including 2 of dexamethasone implant and 1 of methotrexate. No multivariate logistic regression was analyzed.

DBP = diastolic blood pressure; SBP = systolic blood pressure; IVI= intravitreal injection.

cardiovascular events (HR = 1.36 [95% CI, 1.03–2.00]), all-cause mortality (HR = 1.33 [95% CI, 1.07–1.67]), and cardiovascular mortality (HR = 2.09 [95% CI, 1.23–4.48]) compared with normotensive subjects.[16] Stress or anxiety can activate the autonomic nervous system and hypothalamic pituitary adrenal axis and chronic stress can lead to cortisol resistance, and dysregulation of these two systems can induce physical illnesses, such as cardiovascular disease.[10] Although we did not assess anxiety level in our study, the previous studies suggest that stress or anxiety may have caused the perioperative spike in BP.

Unfortunately, there were no published studies to support the stress and anxiety differences between phacoemulsification and IVI. We did not assess stress anxiety level in our retrospective study. We could not support the stressful level between the two procedures, but it is worthwhile to perform a prospective study to evaluate the stress differences between the two procedures. Besides, the surgical time for phacoemulsification usually took longer compared with the IVI procedure; thus, immediate postoperative BP/HR could not well represent perioperative BP, especially in the patients who received cataract surgery. However, studies revealed that stress or anxiety may cause the perioperative BP spike, and preoperative anxiety might cause hemodynamic problems in the intraoperative period. Other studies found transient BP rises, not only in SBP but also in DBP after the procedure.[16] Although we could not support IVI being more stressful than phacoemulsification, higher preoperative BP and perioperative BP in the IVI group reminded us of the increased risk of hypertensive urgency. Thus, it is important to monitor preoperative hypertension, especially for patients at risk of cardiovascular disease.

However, in the present study, patients who are older and have higher rates of diabetes, preexisting hypertension or other vascular diseases may be vulnerable to changes in BP. Patients who received IVIs were older and had higher rates of hypertension and diabetes compared with the control group. A previous study reported that up to 70–80% of patients with diabetes have concomitant hypertension, both of which can lead to significant complications of microvascular diseases, such as retinopathy, nephropathy, and neuropathy.[17,18] In our study, the patients' demographics may explain the higher change in BP in the IVI group. AMD (n = 29), RVO (n = 11), and DME (n = 19) accounted for 84% of the patients in the IVI group. In addition, the patients in the IVI group were older (mean age 72 vs 68 years old, $p = 0.022$) and had a higher rate of diabetes (47.1% vs 22.3%, $p = 0.001$). Preexisting hypertension may be a risk factor for hypertensive urgency, which in turn may be a risk factor for cardiovascular or cerebrovascular effects. Thus, it reminds physicians to pay more attention to patients with more comorbidities.

In a meta-analysis for patients with DME,[7] the authors reported a higher rate of side effects in those with the highest exposure. A higher risk of death was reported in the patients who received monthly injections of aflibercept or ranibizumab for 2 years compared with those who received sham and laser therapies (total 1078 patients, OR 2.98, 95% CI 1.44–6.14, $p = 0.003$). Although the study did not adjust for patient baseline characteristics and the possible mechanisms, most of the deaths occurred after a full year of monthly injections. This suggests that intensive treatment may increase the risk of death. Although we included once in multiple injections to reduce the bias from the same patients, it was significant that perioperative SBP (T1) was significantly increased before and after IVIs when repeated injections were also included (mean SBP T0 = 142.10 mmHg, mean SBP T1 = 159.43 mmHg, mean SBP T2 = 139.00 mmHg, $p < 0.001$ between T0 and T1, $p < 0.001$ between T1 and T2). Taken together, these findings suggest that it is important to reduce procedure-related risks in patients with more comorbidities.

There are several limitations to this study. First, BP and HR measurement could be influenced by multiple factors, such as white-coat effects and body position during measurements. To eliminate the disadvantages, in our operation waiting room, we routinely asked patients to rest before BP/HR measurement. Automated sphygmomanometer provided good reproducibility and self-measurement in the same sitting position reduced the possibility of white-coat effect and body position effect.[19] Secondly, we recorded BP and HR immediately after the procedure and designated them as perioperative BP/HR. However, the surgical time for phacoemulsification usually took longer compared with the IVI procedure; thus, immediate postoperative BP/HR could not well represent perioperative BP, especially in the patients who received cataract surgery. Thirdly, repeated injections might cause confounding bias. Berger et al[16] mentioned discomfort after the last injection ($R = 0.311$; $p = 0.02$) was associated with an elevated perioperative SBP,

but the number of previous injections had no association. To reduce the confounding of repeated exposure, it is better to include naive cases, which means the first injection. However, to include naive cases only is difficult in a retrospective study because a small number of cases might decrease the statistical power. To reduce the bias of repeated injection, we randomly chose one set of data in patients with multiple injections during study period.

Besides, the case number is relatively small in this series, the statistic power maybe insufficient and some bias may exist when we performed the multivariate analysis. Finally, all enrolled patients were from a single tertiary referral center, and all surgeries/procedures were done in the operation room. Thus, our findings may not be extrapolated outside this study setting.

Taken together, our study suggests that IVI can cause transient elevations of BP. In our clinical practice, patients with hypertensive emergency were forbidden from surgeries and medical treatment commenced immediately. Patients presenting raised preoperative SBP higher than 200 mmHg without symptoms received medication therapy. Patients with preoperative SBP less than 200 mmHg without systemic symptoms underwent surgeries as scheduled. However, based on our results, the risk of hypertensive urgency may be higher in patients with hypertension and elevated preoperative SBP. We might modify our clinical practice and pay more attention to patients with more comorbidities. Long-term BP control would be suggested.

In conclusion, our results suggest that temporal fluctuations in BP and HR should be monitored, especially in patients at risk. Elevated preoperative SBP may be a warning sign of hypertensive urgency, especially in patients with preoperative SBP ≥160 mmHg (OR 17.89, compared with the group of preoperative SBP <140 mmHg). Despite satisfactory safety of IVIs, physicians should pay more attention to patients with more comorbidities. Our results suggested that new medications with a longer duration may not only reduce the treatment burdens from patients and medical providers but also potentially reduce the cardiovascular risk related to the procedure itself.

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REFERENCES

1. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Cochrane Database Syst Rev* 2014: CD005139.
2. Wang W, Lo ACY. Diabetic Retinopathy: Pathophysiology and Treatments. *Int J Mol Sci* 2018;**19**:E1816.
3. Campa C, Alivernini G, Bolletta E, Parodi MB, Perri P. Anti-VEGF therapy for retinal vein occlusions. *Curr Drug Targets* 2016;**17**:328–36.
4. Willis J, Morse L, Vitale S, Parke DW 2nd, Rich WL, Lum F, et al. Treatment patterns for myopic choroidal neovascularization in the United States: analysis of the IRIS registry. *Ophthalmology* 2017;**124**:935–43.
5. Cunningham MA, Edelman JL, Kaushal S. Intravitreal steroids for macular edema: the past, the present, and the future. *Surv Ophthalmol* 2008;**53**:139–49.
6. Robinson ES, Khankin EV, Karumanchi SA, Humphreys BD. Hypertension induced by vascular endothelial growth factor signaling pathway inhibition: mechanisms and potential use as a biomarker. *Semin Nephrol* 2010;**30**:591–601.
7. Avery RL, Gordon GM. Systemic safety of prolonged monthly anti-vascular endothelial growth factor therapy for diabetic macular edema: a systematic review and meta-analysis. *JAMA Ophthalmol* 2016;**134**:21–9.
8. Fung AE, Rosenfeld PJ, Reichel E. The international intravitreal bevacizumab safety survey: using the internet to assess drug safety worldwide. *Br J Ophthalmol* 2006;**90**:1344–9.
9. Godoy LD, Rossignoli MT, Delfino-Pereira P, Garcia-Cairasco N, de Lima Umeoka EH. A comprehensive overview on stress neurobiology: basic concepts and clinical implications. *Front Behav Neurosci* 2018;**12**:127.
10. Dimsdale JE. Psychological stress and cardiovascular disease. *J Am Coll Cardiol* 2008;**51**:1237–46.
11. Golbidi S, Frisbee JC, Laher I. Chronic stress impacts the cardiovascular system: animal models and clinical outcomes. *Am J Physiol Heart Circ Physiol* 2015;**308**:H1476–98.
12. Torpy JM, Burke AE, Glass RM. Acute emotional stress and the heart. *JAMA* 2007;**298**:360.
13. White WB, Berson AS, Robbins C, Jamieson MJ, Prisant LM, Roccella E, et al. National standard for measurement of resting and ambulatory blood pressures with automated sphygmomanometers. *Hypertension* 1993;**21**:504–9.
14. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;**311**:507–20.
15. Ueta T, Noda Y, Toyama T, Yamaguchi T, Amano S. Systemic vascular safety of ranibizumab for age-related macular degeneration: systematic review and meta-analysis of randomized trials. *Ophthalmology* 2014;**121**:2193–203.e1–7.
16. Berger V, Munk MR, Lersch F, Wolf S, Ebneter A, Zinkernagel MS. Association of intravitreal injections with blood pressure increase: the following excitement and anxiety response under intravitreal injection study. *JAMA Ophthalmol* 2019;**137**:87–90.
17. Long AN, Dagogo-Jack S. Comorbidities of diabetes and hypertension: mechanisms and approach to target organ protection. *J Clin Hypertens (Greenwich)* 2011;**13**:244–51.
18. Piette JD, Kerr EA. The impact of comorbid chronic conditions on diabetes care. *Diabetes Care* 2006;**29**:725–31.
19. Ogedegbe G, Pickering T. Principles and techniques of blood pressure measurement. *Cardiol Clin* 2010;**28**:571–86.