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The association between myocardial infarction and intravitreal bevacizumab injection

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Abstract

To evaluate the risk of myocardial infarction (MI) after receiving intravitreal bevacizumab (IVB) injection. We retrospectively reviewed the charts of patients who had received IVB injection in 2016, and grouped them according to whether they received the injection for age-related macular degeneration (AMD), diabetes-related complications, or retinal vein occlusion (RVO). We then investigated the prevalence of MI within 2 months after IVB injection and analyzed the possible association of IVB with MI. During 2016, 724 patients were enrolled and received a total of 1870 IVB injections. Seven patients were diagnosed with MI within 2 months after receiving an IVB injection. Of 274 patients with AMD, 2 were diagnosed with MI; of 311 patients with diabetes-related complications, 3 were diagnosed with MI; and of 139 patients with RVO, 2 were diagnosed with MI ($P = 0.785$). All MIs occurred between 3 days and 3 weeks after IVB injection (mean $= 14.00 \pm 6.45$ days). The MIs after receiving IVB were associated with previous history of MI or cerebrovascular infarction in multivariate logistic regression analysis ($P = 0.005$). There was no significant difference in MI prevalence after IVB injection according to the reason for receiving the injection. However, care should be taken when administering IVB injections, especially to patients with risk factors such as history of MI or cerebrovascular infarction.

Abbreviations: AMD = age-related macular degeneration, BRB = blood-retinal barrier, CVA = cerebrovascular accident, DM = diabetes mellitus, DME = diabetic macular edema, IVB = intravitreal bevacizumab, ME = macular edema, MI = myocardial infarction, OCT = optical coherence tomography, PDR = proliferative diabetic retinopathy, ROP = retinopathy of prematurity, RVO = retinal vein occlusion, VEGF = vascular endothelial growth factor.

Keywords: age-related macular degeneration, bevacizumab, intravitreal injection, myocardial infarction, retinal vein occlusion

1. Introduction

Anti-vascular endothelial growth factor (VEGF) has become the main treatment to reduce vascular leakage and to regress neovascularization for patients with age-related macular degeneration (AMD). In addition, its use has been expanded to treat diabetic complications, such as proliferative diabetic retinopathy (PDR) with vitreous hemorrhage and diabetic macular edema (DME), retinal vein occlusion (RVO), and retinopathy of prematurity (ROP).[1–6]

Bevacizumab is an anti-VEGF agent that has been approved by the Food and Drug Administration (FDA) to treat colorectal cancer and glioblastoma,[7,8] but not as an intravitreal injection.[9] Ranibizumab was approved by the FDA in 2006 for the

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treatment of AMD, in 2010 for the treatment of RVO, and in 2012 for the treatment of DME.[9,10] Aflibercept was approved by the FDA in 2011 for the treatment of AMD, and 2014 for the treatment of DME.[9,11]

Despite use being off label, intravitreal bevacizumab (IVB) is often used because of its cost-effectiveness, and is also inevitably used without FDA approval because of its effectiveness for PDR vitreous hemorrhage with or without vitrectomy, neovascular glaucoma, and ROP.[6,9,12–14] However, IVB injection has side effects, such as worsening of the epiretinal membrane, subretinal fibrosis or tractional retinal detachment, and an increased risk of thromboembolism.[15–20] There has also been controversy regarding the possible association between bevacizumab and thromboembolic events. Some studies reported no association between bevacizumab injection and myocardial infarction (MI),[21–25] while others did report a relationship.[18–20] In the present study, patients were grouped according to their reasons for receiving IVB injections, and the possible association between IVB injection and MI prevalence within 2 months was analyzed.

2. Methods

The medical records of all patients treated with IVB injections during 2016, at St Vincent Hospital, Suwon, Republic of Korea, were reviewed retrospectively. This study was performed according to the tenets of the Declaration of Helsinki, and the study protocol was approved by the institutional review/ethics board of the Catholic University of Korea, St Vincent's Hospital. Informed consent was not obtained because this study involved the review of patient records.

All patients underwent a full ophthalmic examination that included a dilated fundus examination and optical coherence

tomography (OCT) (Cirrus High Definition-OCT; Carl Zeiss Meditec, Dublin, CA). The MI was diagnosed using serum cardiac biomarkers and an electrocardiogram, and all patients with MI were treated with percutaneous coronary intervention after the MI diagnoses.

Inclusion criteria included receiving IVB injection because of AMD, diabetes-related complications such as PDR with vitreous hemorrhage or center-involved DME, and macular edema (ME) because of RVO. Patients were injected with 1.25 mg of bevacizumab, irrespective of the type of disease,[26,27] and were diagnosed with MI within 2 months after the IVB injection. We checked all the patients twice at 1 and 2 months after IVB. We excluded patients who were not followed-up until 2 months after the injection, or had incomplete data about medical history.

The Kruskal–Wallis test was used to compare age and the number of injections among the 3 groups. Tukey's post hoc analysis was used to compensate for multiple statistical analyses and comparisons. The chi-square test and Fisher's extract test were used to compare the distribution of sex and the prevalence of MI among the groups. And the logistic regression was used to find out the association of risk factors and MIs after IVBs.

Statistical analyses were performed using R software (ver. 3.2.3; [2015-12-10; platform, x86_64-redhat-linux-gnu, R Core Team, 2015]). The R software was a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria; URL https://www.R-project.org/). The statistical significance level was set at $P < 0.05$.

3. Results

After excluding 37 patients with incomplete records within 2 months after the IVB injection, we enrolled 724 patients, who received a total of 1870 IVB injections. The average age was 62.09 ± 13.39 years. The average age of the diabetes mellitus (DM) group was 56.21 ± 11.60 years, which was significantly younger than the AMD group (69.91 ± 11.74 years; $P < 0.001$) and the RVO group (65.01 ± 12.38 years; $P < 0.001$). There was also significant difference in age between the AMD and RVO groups ($P < 0.001$). There were 386 males and 338 females, and there was a significant difference in sex distribution among the 3 groups ($P = 0.015$); post hoc analyses showed significant difference between the AMD and RVO groups ($P = 0.013$). The average number of injections was 2.58 ± 1.60. The number of IVB injections was significantly different among the 3 groups ($P < 0.001$). The post hoc analyses showed that the average number of IVB injections in patients with AMD (2.98 ± 1.57) was significantly higher than in patients with DM (2.55 ± 1.72; $P < 0.001$) and patients with RVO (1.88 ± 1.00, $P < 0.001$). There was also significant difference in the average number of IVB injections between patients with DM and RVO ($P = 0.001$).

Seven patients were diagnosed with MI within 2 months after receiving an IVB injection. Of 274 patients with AMD, 2 (0.73%) were diagnosed with MI; of 311 patients with diabetes-related complications, 3 (0.96%) were diagnosed with MI; and of 139 patients with RVO, 2 (1.44%) were diagnosed with MI. There was no significant difference in MI prevalence after IVB injection according to the reason for receiving the injection ($P = 0.785$; Table 1).

The average age of patients diagnosed with MI after the IVB injection was 64.42 ± 13.22 years (6 males and 1 female). All patients experienced chest pain between 3 and 21 days after the IVB injections. The average time of onset of these pains was 14.00 ± 6.45 days. Four patients were treated with hypertension

Table 1

Demographic and baseline clinical characteristics of the patients.

	AMD (n=274)	DM (n=311)	RVO (n=139)	P-value
Age (years)	69.91±11.74	56.21±11.60	65.01±12.38	<0.001
Sex (male:female)	154:120	172:139	60:79	0.015
Average injections of IVB	2.98±1.57	2.55±1.72	1.88±1.00	<0.001
Total number of IVB	4.96±3.33	3.67±3.13	2.50±1.41	<0.001
Number of MI (prevalence)	2 (0.73%)	3 (0.96%)	2 (1.44%)	0.785

AMD=age-related macular degeneration, DM=diabetes mellitus, IVB=intravitreal bevacizumab, MI=myocardial infarction, RVO=retinal vein occlusion.

medications and 5 were treated for DM. Five patients were diagnosed with MI after receiving the first injection and the other 2 patients were diagnosed after the third injection. Two of these patients had a history of MI and 1 had a history of cerebrovascular infarction. In logistic regression analysis, MIs after receiving IVB were associated with previous history of MI or cerebrovascular infarction ($P = 0.005$; Table 2).

4. Discussion

As previously mentioned, there has been controversy concerning the possible association between IVB injections and thromboembolic accidents. Some studies reported no association between IVB injections and cerebrovascular accidents (CVAs) or MIs,[21–25] but others reported that IVB injections were associated with an increased risk of CVAs or MIs.[18–20,28,29] These studies reported that the cause of the MIs was the use of anti-VEGF treatments that increased the risk of systemic VEGF suppression.[28,30] Some studies have also reported a significant decrease in plasma VEGF levels after bevacizumab or aflibercept intravitreal injections,[31,32] and the presence of ranibizumab in the systemic circulation after intravitreal injections.[33] The VEGF is necessary for normal functioning of the endothelium, where it promotes vascular integrity and endothelial cell survival,[34,35] but in 1 study systemic anti-VEGF agents caused vascular endothelial cell dysfunction, which induced a coagulation cascade.[36] Another study showed that IVB injection resulted in increased serum D-dimer levels and risk of thromboembolism.[37] Some VEGF isoforms play a positive role in cardiovascular function, but nonselective inhibition of VEGF may be involved in the induction of MI.[38] Most of these studies investigated patients with AMD[18,21,22,27,39]; the present study is the first to compare differences in vascular complication according to the type of disease treated with anti-VEGF.

Table 2

Variables associated with MI to IVB upon logistic regression analysis.

	Univariate analysis		Multivariate analysis	
	Adjusted OR (95% CI)*	P-value	Adjusted OR (95% CI)*	P-value
IVB during a year	0.94 (0.52-1.43)	0.797		
Total number of IVB	1.01 (0.75-1.22)	0.955		
DM	2.00 (0.43–14.06)	0.408		
Hypertension	1.92 (0.42–9.80)	0.396		
History of CVA or MI	10.01 (1.93–46.59)	0.003	9.05 (1.73–42.55)	0.005

CI=confidence interval, CVA=cerebrovascular infarction, DM=diabetes mellitus, IVB=intravitreal bevacizumab, MI=myocardial infarction, OR=odds ratio.
* Adjusted by age and sex.

We could not determine the significance of group differences in prevalence of MI, because of the small sample size. The prevalence of MI was 0.73% in patients with AMD, 0.96% in patients with DM, and 1.44% in patients with RVO. Of the 3 groups, the average number of injections was lowest in the patients with RVO, and the average age of the patients with RVO was lower than that of the patients with AMD. In addition, the patients with RVO included a higher proportion of females compared with the other groups. Previous studies have reported a higher prevalence of MI among males than among females in the Korean population.[40,41] Despite these demographic characteristics of the RVO group, the difference in MI prevalence between the AMD and RVO groups was 0.71%, with a 1.97-fold higher rate of MI development in the RVO group compared with the AMD group, although this difference was not significant ($P=0.605$). Although the small sample size precluded significance, there was a larger difference in prevalence than we expected. This may indicate that there is no association between IVB injection and the development of MI, not only because there was no significant difference but also because more MIs occurred in patients with DM and RVO, suggesting that the MI was caused by systemic vascular disorders and not by IVB injections. However, it is also possible that DM- or RVO-induced damage to the blood-retinal barrier (BRB) could have affected the systemic circulation and induced vascular damage. A previous study reported that plasma VEGF levels among patients with DME were decreased compared with those in patients with AMD after IVB injections, and that this decrease was maintained for 1 month.[31] The study did not suggest why plasma VEGF levels among patients with DME were lower than those of patients with AMD, but based on the results of our study, we suggest that damage to the BRB may have played a role. It is well known that retinal leakage after breakdown of the BRB and subsequent ME are caused by diabetic retinopathy, AMD, RVO, and uveitis.[42] Although there has been a report of AMD associated with BRB damage,[43] there is a lack of evidence.[44] However, BRB damage associated with DM or ischemic retinal diseases such as RVO is well established.[42,45–49] Furthermore, the patients with RVO with MI were all diagnosed with ischemic central RVO, which is a more severe ischemic retinal condition. Damage to the BRB in patients with DM and RVO could induce a decrease in VEGF levels, which could in turn induce MI. This possibility should be investigated using a prospective design that determines systemic levels of VEGF and anti-VEGF in patients with AMD, RVO, and DM.

A previous study of the prevalence of MI among patients with DM reported 54.62 cases/10,000 per year among the Korean population in 2012 to 2013.[41] This differed from the present study, which showed a prevalence of 106.76/10,000, although the study period and the status of the enrolled patients were not the same. In general, DM retinopathy is associated with a long disease duration, poor glycemic control, and comorbidities such as hypertension and nephropathy.[50–52] In addition, one of the patients with DME already had a history of MI, so the comparison was not valid.

Previous studies reported only the prevalence of MI, but we investigated the interval between IVB injections and the development of MI. All patients had chest pains between 3 and 21 days after the IVB injection. Previous animal pharmacokinetic studies after IVB injection reported that bevacizumab reached maximal levels in the retina at 7 days after injection, then decreased over 30 days.[53] One study reported that after the first IVB injection, the median time to reach maximum systemic levels was 7.0 days, and when comparing bevacizumab, ranibizumab, and aflibercept, bevacizumab showed the highest systemic levels in patients with AMD.[54] Another study reported that VEGF levels were significantly reduced until 28 days after IVB injection in exudative patients with AMD, suggesting a possible systemic safety issue.[55] Overall, these studies showed that the systemic effect of IVB injection reached a maximum at 1 week after injection, then decreased over 1 month. All of the MIs in our patients occurred between 3 and 21 days after the IVB injection, and most occurred between 11 and 21 days, with no occurrences between 1 and 2 months after the injection. This analysis included previous studies that reported the presence of systemic bevacizumab, suggesting a systemic effect of MI caused by IVB injection.

This study had some limitations. First, the sample size was not large enough to obtain definitive results. Second, investigation of the loss of patients to follow-up should have been performed, because these losses may have been associated with thromboembolism. Prospective studies with larger sample populations would therefore be of benefit.

Although most previous studies characterized patients with AMD, characterization of systemic VEGF and anti-VEGF levels in patients with DM and RVO could help to determine the extent of BRB damage, and identify the possible association between MI and IVB injections.

In conclusion, there was no significant difference in MI prevalence according to the type of disease that required IVB injections. The MIs after receiving IVB were associated with previous history of MI or cerebrovascular infarction. Additionally, considering that all MIs developed within 3 weeks after the IVB injections, careful consideration by clinicians is necessary before administering IVB injections, especially to patients who have MI risk factors.

Author contributions

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