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Analysis of factors associated with short-term elevation of intraocular pressure after Conbercept intravitreal injection

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康柏西普玻璃体腔注射后患眼短期眼压升高的影响因素分析

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摘要

目的:探讨分析玻璃体腔注射康柏西普后短期眼压(IOP)升高的影响因素。

方法:临床前瞻性观察研究。共纳入玻璃体腔注射康柏西普的视网膜病变患者 269 例 269 眼,所有患眼均行康柏西普玻璃体腔注射治疗。其中,男 143 例,女 126 例;年龄相关性黄斑变性(ARMD)患者 201 例,其他类型视网膜变性患者 68 例。平均年龄 62.86±11.74 岁,采用非接触气动式眼压计,分别在注射前,注射后 10、30min,2 和 4h 对患者进行 IOP 测量。根据注射后 10min IOP 升高情况来进行分组,IOP 升高 10 mmHg 及以上定义为 IOP 升高组,IOP 升高小于 10 mmHg 定义为 IOP 稳定组。采用多因素 Logistic 回归分析分析两组之间的差异。

结果:患者在注射后 10、30min,2 和 4h 的平均 IOP 分别为 24.1、20.2、19.5、16.9 mmHg,注射后各个时间点的 IOP 较注射前平均升高 6.7、3.1、1.7、0.5 mmHg。其中,IOP 高组 56 例,IOP 稳定组 213 例。两组患者年龄、最佳矫正视力(BCVA)、性别、眼别、疾病类型比较均无统计学差异(均 $P>0.05$);注药次数($Z=-4.389$, $P=0.012$)、注射前 IOP 及注射后各时间点的 IOP($t=-5.343$, -10.467, -8.933, -6.124, -4.635,均 $P<0.01$)比较差异均有统计学差异。多变量 Logistic 回归分析显示,基础 IOP 与注射后 10min IOP 升高呈正相关($B=-0.913$, $OR=0.521$, 95%CI: 0.211~0.694, $P=0.011$)。

结论:基线 IOP 水平越高,注射后 IOP 升高的风险越高。基线 IOP 是影响玻璃体腔注射康柏西普后患眼短期 IOP 升高的主要相关因素,而注射次数可能是另一个风险因素。

关键词:康柏西普;璃体腔注射;高眼压;影响因素

Abstract

• AIM: To investigate the factors associated with short-term elevation of intraocular pressure (IOP) after conbercept intravitreal injection.

• METHODS: This study was a clinical prospective observational study. It enrolled in 269 eyes of 269 patients who were diagnosed retinopathy, and all patients receive conbercept intravitreal injection. Among them, 143 were males and 126 were females. There were 201 cases of age-related macular degeneration (ARMD) and 68 cases of other retinopathy patients. The mean age was 62.86±11.74 years. Non-contact pneumatic tonometer was used to measure the IOP of the patients before, 10, 30min, 2 and 4h after injection. The group was divided according to the IOP elevation 10min after injection. The IOP elevation 10 mmHg and above was defined as the IOP elevation group, and the IOP elevation less than 10 mmHg was defined as the IOP stable group. Multivariate Logistic regression analysis was used to analyze the differences between the two groups.

• RESULTS: The average IOP of patients at 10, 30min, 2 and 4h after injection was 24.1, 20.2, 19.5 and 16.9 mmHg, respectively. The average IOP at each time point after injection was 6.7, 3.1, 1.7 and 0.5 mmHg higher than that before injection. Among them, 56 cases of increased IOP, 213 cases of stable IOP. There were no significant differences in age, best corrected visual acuity (BCVA), gender, eye side and disease type between two groups (all $P>0.05$). There were statistically significant differences in the number of injection ($Z=-4.389$, $P=0.012$), IOP before injection and IOP at each time point after injection

(t=-5.343, -10.467, -8.933, -6.124, -4.635, all P<0.01). Multivariate Logistic regression analysis showed that baseline IOP was positively correlated with IOP increase 10min after injection (B=-0.913, OR=0.521, 95%CI: 0.211-0.694, P=0.011).

• CONCLUSION: The higher the baseline IOP, the higher risk of elevated IOP after injection. The factor associated with a short-term increase in IOP after intravitreal injection of conbercept was baseline IOP. The number of injection may be another risk factor.

• KEYWORDS: Conbercept; intravitreal injection; ocular hypertension; influencing factor
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INTRODUCTION

Intravitreal ranibizumab and conbercept are anti-vascular endothelial growth factor (anti-VEGF) agents used to treat choroidal neovascularization and retinal vascular disorders with rarely reported ocular adverse events such as intraocular inflammation, retinal tears, vitreous hemorrhage, endophthalmitis, lens changes, and intraocular pressure (IOP)[1-2]. As expected, volume driven acute ocular hypertension occurs immediately after intravitreal injection, but this increase in IOP is usually transient and easily tolerated. Some recent reports show that the continuous high IOP after each injection is different from the short-term acute high IOP, and it is also related to repeated intravitreal injection of anti-VEGF[3-4].

Treatment with intravitreal injection results in more fluid entering the intravitreal and may cause an increase in acute IOP. Transient and short-term increases in IOP following intravitreal anti-VEGF therapy have been well described in previous reports[5]. However, anti-VEGF therapy may also lead to long-term and sustained elevated IOP. There are many risk factors for chronic ocular hypertension caused by anti-VEGF treatment, including total injection times, high injection frequency, previous glaucoma and so on[1,6]. Here, we reported 269 eyes with short-term elevation IOP after conbercept intravitreal injection, and to investigate the influence factors of short-term IOP after conbercept intravitreal injection.

SUBJECTS AND METHODS

Patients This study was a clinical prospective observational study. This study enrolled in 269 eyes of 269 patients who were diagnosed retinopathy, and all patients receive conbercept intravitreal injection in our hospital from July 2018 to July 2019 were enrolled. There were 143 males and 126 females. There were 201 cases with age-related macular degeneration (ARMD) and 68 cases with other retinopathy patients. The average age was 62.86±11.74 years. The diagnosis was determined according to the fundus examination and fluorescein angiography. Inclusion criteria: 1) >18 years old; 2) Recent onset (<1.5mo); 3) No family history or history of glaucoma; 4) Follow up ≥ 1mo; Exclusion criteria: 1) Baseline IOP >21mmHg; 2) Axial length >26.00 mm or < 22.00 mm; 3) Vitrectomy or other intraocular surgeries within half a year; 4) Other related diseases. This study followed the principles of the Helsinki Declaration and was approved by the Hospital Ethics Committee. The subject has been informed of the written consent of the study.

Surgical and IOP Measurements All patients underwent slit-lamp microscopy, IOP, best corrected visual acuity (BCVA), fundus angiography and optical coherence tomography angiography (OCTA) before surgery, which were performed by two experienced clinicians. The eye was treated with antibiotic eye drops 3d before injection. After surface anesthesia, conventional disinfection towel was used, 30G injection needle was used, 4.0 mm behind the edge of hornsclera below the temporal, vertical injection, and slowly injected 0.05 mL of conbercept (0.5 mg/0.05 mL). Non-contact pneumatic tonometer (NT-4000, NIDEK; Japan) was used to measure the IOP of patients before and after injection at 10, 30min, 2 and 4h, respectively. According to the reference[7], we divided the patients into the IOP elevation group and the IOP stable group according to whether the IOP elevation exceeded 10 mmHg at 10min after vitreous cavity injection.

Statistical Analysis Statistical analysis was performed using SPSS22.0. Continuous variables were displayed as $\bar{x} \pm s$, categorical variables were displayed as the number of subjects and its percentage. The differences between continuous variables were tested by independent t test, and categorical variables were tested by Chi-square test. Equal group covariance study design was used. Chi-square test was used to compare gender, eye side and disease type between IOP elevation group and IOP stable group. Two-way ANOVA was used to compare IOP at different time points between IOP elevation group and IOP stable group, and LSD-t test was used for pairwise comparison between groups. Univariate analysis was used for correlation factor analysis, and then Logistic regression was used for multivariate analysis to determine whether the independent variable (baseline IOP and total number of injection) was still associated with the dependent variable (IOP elevation) after controlling the identified confounding factors. Expressed as odds ratio (OR) and 95% confidence interval (CI). P value < 0.05, the difference is considered statistically significant.

RESULTS

Variation of IOP at Each Time Point The mean IOP of the 269 patients in the study was 24.1, 20.2, 19.5 and 16.9 mmHg at 10, 30min, 2 and 4h after the injection, respectively. The IOP at each time point after the injection was 6.7, 3.1, 1.7 and 0.5 mmHg higher than that before the injection, with statistically significant differences (P<0.01).

The number of eyes with IOP increased by more than 10 mmHg at each time point after surgery was 56 (20.8%), 15 (5.6%), 10 (3.7%), and 3 (1.1%), respectively. At 10min after injection, IOP in 9 eyes (3.4%) increased to more than 20 mmHg, all patients recovered to the preoperative level 4h after the operation, and no obvious abnormal IOP was observed in the follow-up observation for 1mo. It is worth mentioning that 5 of the 9 patients received more than 8 injections in total and 4 patients received more than 5 injections.

Analysis of Influencing Factors In 269 eyes of the 269 patients included in the study, 56 eyes in the group with elevated IOP and 213 eyes in the group with stable IOP were included. And the history of glaucoma was excluded in the 56 patients with elevated IOP during follow-up. Two-way ANOVA was used to compare IOP at different time points between IOP elevation group and IOP stable group. There was significant difference in IOP at different time points (F_{times} = 494.197, P<0.01). There was significant difference in IOP between the two groups (F_{groups} = 106.452, P<0.01). There was no significant difference in age, BCVA (t = -1.634, -0.056, all P>0.05), gender, side and disease type (χ^2 = 2.110, 3.143, 2.235, all P>0.05) between the two groups. The number of injection (Z = -4.389, P = 0.012), baseline IOP and IOP at each time point after injection (t = -5.343, -10.467, -8.933, -6.124, -4.635, all P<0.01) showed statistically significant differences (Tables 1 and 2). Multivariate and univariate Logistic regression analysis was performed on the significant factors (number of injection and baseline IOP). Finally, there was no statistical difference in the number of injection (B = -1.343, OR = 1.189, 95%CI: 0.921-2.342, P = 0.121), and the baseline IOP was positively correlated with the increase of IOP 10min after injection (B = -0.913, OR = 0.521, 95%CI: 0.211-0.694, P = 0.011; Table 3).

DISCUSSION

Although the use of anti-VEGF drugs has increased in clinical practice, long-term safety data are still being published. The main studies on the complications of anti-VEGF treatment are mostly limited to intraocular inflammation, retinal tear, vitreous hemorrhage, endophthalmitis and lens changes. However, elevation of IOP was not found to be a complication of intravitreal injection[8-9]. With the injection of liquid into the vitreous cavity, the instantaneous increase of IOP is a phenomenon reported in the literature. Several published reports showed that IOP recovered to 25 mmHg within 30-60min after intravitreal anti-VEGF treatment, but it did not need IOP-lowering therapy[10-11]. Transient ocular hypertension immediately after intravitreal injection is a very common phenomenon, but some reports suggest that sustained high IOP after intravitreal injection of anti-VEGF is also possible[12].

At present, the anti-VEGF drugs that have been clinically approved for the treatment of neovascular ARMD and other retinopathy include pegaptanib, ranibizumab and aflibercept. There are some differences in the approved drugs all over the world. At the end of 2013, Chengdu Kanghong Pharmaceutical Group was approved by China Food and Drug Administration to use conbercept in the treatment of neovascular ARMD in China[13]. Conbercept, also known as KH902 (Chengdu Kanghong Biotechnology Co., Ltd.; Sichuan, China), is a recombinant fusion protein similar with aflibercept. It is a receptor bait composed of the second Ig domain of VEGFR-1, the third and fourth Ig domains of VEGFR-2 and the constant region (FC) of human IgG1[14]. There are some differences between conbercept and aflibercept in structure. The molecular weight of conbercept is larger, and there is one more fourth binding domain of VEGFR-2 than aflibercept. Compared with aflibercept, it has the characteristics of lower VEGF dissociation rate, higher binding affinity, lower adhesion to extracellular matrix and lower isoelectric point. As a result, it has a long clearing time[15]. Conbercept is well tolerated in clinical trials and provides visual results similar with other anti-VEGF drugs.

Previous studies have reported that eyes treated with intravitreal injection of ranizumab or bevacizumab may have sustained ocular hypertension. The probability of sustained ocular hypertension is between 3.5% and 6%, and the level of sustained ocular hypertension is between 22-58 mmHg[16-17]. This paper reports 269 patients with short-term elevated IOP after intravitreal injection of conbercept, and discusses the factors related to short-term elevated IOP. Our study showed that increased IOP after vitreous cavity injection was independent of disease, age and gender. This is consistent with the research results of Atchison *et al*[18]. However, some researchers believe that the increased IOP after vitreous cavity injection has a certain correlation with the disease type and age, and this conclusion needs to be verified by further studies. According to Kim *et al*[19], the IOP of glaucoma patients injected with the anti-VEGF preparation in the glass body cavity is much higher than that of patients with normal IOP, and it takes longer for the IOP to return to the normal level. Whether glaucoma is a risk factor for increased IOP after vitreous cavity injection or not, the large fluctuation of IOP caused by repeated injections may cause great damage to the optic nerve, and therefore should be paid more attention by ophthalmologists. The results of this study showed that the baseline IOP was the main risk factor for the short-term IOP increase after the vitreous cavity injection of conbercept. The higher baseline IOP, the higher risk to gain elevation of IOP after injection.

At 10min after injection, the IOP increased to over 20 mmHg in 9 eyes, and there were 5 of the 9 patients received more than 8 injections in total and 4 patients received more than 5 injections. It is speculated that the number of injections may be related to increased IOP. In the univariate analysis, the number of injections was associated with increased IOP (P < 0.01). But in the multifactor analysis, the number of

Table 1 The comparison of IOP at different time points in affected eyes ($\bar{x}\pm s$, mmHg)

Groups	Eyes	IOP				
		Before injection	10min after injection	30min after injection	2h after injection	4h after injection
IOP elevation group	56	18.63±4.31	33.31±6.33	25.46±6.23	20.11±6.27	18.39±5.25
IOP stable group	213	16.54±4.33	21.27±5.69	17.19±5.60	16.64±6.61	16.22±5.51
t		−5.343	−10.467	−8.933	−6.124	−4.635
P		<0.01	<0.01	<0.01	<0.01	<0.01

IOP: Intraocular pressure.

Table 2 The parameters of the two groups

Parameters	IOP elevation group	IOP stable group	$t/\chi^2/Z$	P
Eyes	56	213		
Age ($\bar{x}\pm s$, year)	63.25±10.87	62.47±13.56	−1.634	0.367
Geder (M/F, cases)	32/24	111/102	2.110	0.245
Side (Right/Left, eyes)	30/26	109/104	3.143	0.132
Disease type (ARMD/Others, eyes)	40/16	161/52	2.235	0.213
BCVA ($\bar{x}\pm s$, LogMAR)	0.66±0.43	0.69±0.49	−0.056	0.902
Number of injection ($\bar{x}\pm s$, times)	4.25±1.79	2.43±1.33	−4.389	0.012
Baseline IOP ($\bar{x}\pm s$, mmHg)	18.63±4.31	16.54±4.33	−5.343	0.009

IOP: Intraocular pressure; ARMD: Age-related macular degeneration.

Table 3 The COX analysis of factors affecting IOP after vitreous cavity injection

Parameters	IOP					
	Univariate analysis			Multifactor analysis		
	OR	95%*CI*	*P*	*OR*	95%*CI*	*P*
Age	0.825	0.445-1.558	0.571			
Gender	0.918	0.380-2.154	0.834			
Side	0.551	0.257-2.167	1.143			
Disease type	0.635	0.268-1.477	0.274			
BCVA	0.758	0.367-1.537	0.435			
Number of injection	0.653	0.834-7.243	0.005	1.189	0.921-2.342	0.121
Baseline IOP	0.312	0.173-2.156	<0.001	0.521	0.211-0.694	0.011

BCVA: Best corrected visual acuity; IOP: Intraocular pressure.

injection was not associated with increased IOP ($P>0.05$). According to the comprehensive analysis, these conflicting results may be related to the small sample size of this study and the small difference in injection times between the two groups, which needs to be further verified by follow-up studies.

The results of Tseng *et al*[5] indicate that the intravitreal anti-VEGF drugs may affect the pathway of aqueous humor drainage of trabecular mesh, uveal sclera or schlemm tube, and then affect the normal aqueous humor circulation, resulting in increasing IOP. According to the research results of Sniegowski *et al*[20], after repeated injections into the vitreous cavity of anti-VEGF drugs, chronic inflammation and the inflammation of trabecular mesh lead to the obstruction of aqueous humor drainage and increase IOP. In addition, some researchers believe that silicone oil droplets in the injection instrument may deposit in the eyeball after multiple injections, leading to blocked outflow of aqueous humor and sustained IOP elevation[21-22]. Of course, this needs to be verified by further research.

Our research has certain limitations. It mainly includes: first, the sample size is small and the follow-up period is short; Second, the patients we include are not representative of most people; Third, the effect of corneal thickness was not considered in this study. Our results suggest that the main risk factor for short-term IOP elevation after intravitreal anti-VEGF therapy is the baseline IOP level. The higher the baseline IOP level, the higher risk to gain elevation of IOP after injection. A greater frequency of injection may be another risk factor. This provides some hints to clinicians that for patients with high IOP, glaucoma, or a greater number of injections, protective measures should be taken to prevent IOP elevation in advance, and IOP monitoring before and after operation should be taken as a routine examination item. Next, we will conduct a larger sample size and a longer follow-up period for a prospective control study to further verify the results of the study.

REFERENCES

1 Bracha P, Moore NA, Ciulla TA, WuDunn D, Cantor LB. The acute and chronic effects of intravitreal anti-vascular endothelial growth factor injections on intraocular pressure: a review. *Surv Ophthalmol* 2018;63

(3):281-295
2 Nguyen TT, Guymer R. Conbercept (KH-902) for the treatment of neovascular age-related macular degeneration. *Expert Rev Clin Pharmacol* 2015;8(5):541-548
3 Qian TW, Zhao MY, Wan YJ, Li MX, Xu X. Comparison of the efficacy and safety of drug therapies for macular edema secondary to central retinal vein occlusion. *BMJ Open* 2018;8(12):e022700
4 Subramanian ML, Ness S, Abedi G, Ahmed E, Daly M, Feinberg E, Bhatia S, Patel P, Nguyen M, Houranieh A. Bevacizumab *vs* ranibizumab for age-related macular degeneration: early results of a prospective double-masked, randomized clinical trial. *Am J Ophthalmol* 2009;148(6):875-882
5 Tseng JJ, Vance SK, Della Torre KE, Mendonca LS, Cooney MJ, Klancnik JM, Sorenson JA, Freund KB. Sustained increased intraocular pressure related to intravitreal antivascular endothelial growth factor therapy for neovascular age-related macular degeneration. *J Glaucoma* 2012;21(4):241-247
6 Vo Kim S, Fajnkuchen F, Sarda V, Qu-Knafo L, Bodaghi B, Giocanti-Aurégan A. Sustained intraocular pressure elevation in eyes treated with intravitreal injections of anti-vascular endothelial growth factor for diabetic macular edema in a real-life setting. *Graefes Arch Exp Ophthalmol* 2017;255(11):2165-2171
7 Hoang QV, Tsuang AJ, Gelman R, Mendonca LS, Della Torre KE, Jung JJ, Freund KB. Clinical predictors of sustained intraocular pressure elevation due to intravitreal anti-vascular endothelial growth factor therapy. *Retina* 2013;33(1):179-187
8 Bakri SJ, Thorne JE, Ho AC, Ehlers JP, Schoenberger SD, Yeh S, Kim SJ. Safety and efficacy of anti-vascular endothelial growth factor therapies for neovascular age-related macular degeneration: a report by the American academy of ophthalmology. *Ophthalmology* 2019;126(1):55-63
9 Kim JE, Mantravadi AV, Hur EY, Covert DJ. Short-term intraocular pressure changes immediately after intravitreal injections of anti-vascular endothelial growth factor agents. *Am J Ophthalmol* 2008;146(6):930-934
10 Landa G, Amde W, Doshi V, Ali A, McGevna L, Gentile RC, Muldoon TO, Walsh JB, Rosen RB. Comparative study of intravitreal bevacizumab (Avastin) versus ranibizumab (Lucentis) in the treatment of neovascular age-related macular degeneration. *Ophthalmologica* 2009;223(6):370-375
11 Moraru A, Pînzaru G, Moţoc A, Costin D, Brănişteanu D. Incidence of ocular hypertension after intravitreal injection of anti-VEGF agents in the treatment of neovascular AMD. *Rom J Ophthalmol* 2017;61(3):207-211
12 Wingard JB, Delzell D, Houlihan NV, Lin J, Gieser JP. Incidence of glaucoma or ocular hypertension after repeated anti-vascular endothelial growth factor injections for macular degeneration. *Clin Ophthalmol* 2019;13:2563-2572
13 Cai SW, Yang QH, Li XR, Zhang Y. The efficacy and safety of aflibercept and conbercept in diabetic macular edema. *Drug Des Devel Ther* 2018;12:3471-3483
14 Zhang JX, Liang Y, Xie J, Li D, Hu Q, Li XS, Zheng WY, He R. Conbercept for patients with age-related macular degeneration: a systematic review. *BMC Ophthalmol* 2018;18(1):142
15 de Oliveira Dias JR, de Andrade GC, Novais EA, Farah ME, Rodrigues EB. Fusion proteins for treatment of retinal diseases: aflibercept, ziv-aflibercept, and conbercept. *Int J Retina Vitreous* 2016;2:3
16 Morshedi RG, Ricca AM, Wirostko BM. Ocular hypertension following intravitreal antivascular endothelial growth factor therapy: review of the literature and possible role of nitric oxide. *J Glaucoma* 2016;25(3):291-300
17 Leleu I, Penaud B, Blumen-Ohana E, Rodallec T, Adam R, Laplace O, Akesbi J, Nordmann JP. Late and sustained intraocular pressure elevation related to intravitreal anti-VEGF injections: cases requiring filtering surgery (French translation of the article). *J Fr Ophtalmol* 2018;41(9):789-801
18 Atchison EA, Wood KM, Mattox CG, Barry CN, Lum F, MacCumber MW. The real-world effect of intravitreous anti-vascular endothelial growth factor drugs on intraocular pressure: an analysis using the IRIS registry. *Ophthalmology* 2018;125(5):676-682
19 Kim YJ, Sung KR, Lee KS, Joe SG, Lee JY, Kim JG, Yoon YH. Long-term effects of multiple intravitreal antivascular endothelial growth factor injections on intraocular pressure. *Am J Ophthalmol* 2014;157(6):1266-1271
20 Sniegowski M, Mandava N, Kahook MY. Sustained intraocular pressure elevation after intravitreal injection of bevacizumab and ranibizumab associated with trabeculitis. *Open Ophthalmol J* 2010;4:28-29
21 Melo GB, Figueira ACM, Batista FAH, Filho AASL, Rodrigues EB, Belfort R Jr, Maia M. Inflammatory reaction after aflibercept intravitreal injections associated with silicone oil droplets released from syringes: a case-control study. *Ophthalmic Surg Lasers Imaging Retina* 2019;50(5):288-294
22 Bakri SJ, Ekdawi NS. Intravitreal silicone oil droplets after intravitreal drug injections. *Retina* 2008;28(7):996-1001