

Intravitreal injection practice patterns among Chinese ophthalmologists

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Abstract

• **AIM:** To describe the practice patterns of intravitreal injections (IVIs) among ophthalmologists in China.

• **METHODS:** This was a cross-sectional online survey. Ophthalmologists who had performed accumulated more than 100 injections were contacted by the Brightness Center, a hospital-based national network, to complete an anonymous, 24-question, internet-based survey. They were surveyed on practices in injection techniques, pre-, and post-injections procedures.

• **RESULTS:** A total of 333 ophthalmologists from 28 provinces/municipalities/autonomous regions responded to the survey (50.68% response rate). The 91.29% of the respondents evaluated systemic risk factors by medical history, electrocardiogram (ECG) and blood test. All the respondents used pre-injection prophylactic antibiotics. Most checked intraocular pressure (IOP, 99.1%) and blood pressure (96.1%) before injections. A majority of the respondents performed injections in the operating room (98.8%), wore masks (99.7%), gloves (99.4%) and sterile surgical clothing (96.1%), performed topical anesthetics (97.9%), and applied povidone-iodine (95.8%) pre-injection. The 61.26% of the respondents dilated pupil. About half of the respondents (51.05%) performed bilateral injections in the same setting. Superior temporal quadrant (40.54%) was the most frequent site of injection. Around three

quarters used 30-gauge needles. Most respondents (97.9%) measured the site of injection from limbus. More than half (53.45%) performed conjunctiva displacement prior to injection. The 32.43% of the respondents checked IOP post-injection and 87.99% physicians checked hand motion (HM) or counting fingers (CF) after injection, while 36.94% observed optic nerve perfusion. All participants used topical antibiotics post-injections. Most physicians (91.89%) reviewed patients on the following day.

• **CONCLUSION:** This study provides a description of the real-world practice patterns in IVIs in China and offers critical information regarding education and training of ophthalmologists and amendment of local society guidelines.

• **KEYWORDS:** intravitreal injections; practice pattern; topical antibiotics; Chinese ophthalmologists

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INTRODUCTION

Intravitreal injections (IVIs) have become the most widely performed intraocular procedures with increasing numbers of practices every year. IVIs with anti-vascular endothelial growth factor (VEGF) agents have revolutionized the treatment and prognosis of a variety of retinal and choroidal diseases, including age-related macular degeneration, diabetic macular edema, proliferative diabetic retinopathy, retinal vein occlusion, choroidal neovascularization, retinopathy of prematurity, and other ocular disorders. It is reported that over 4 million IVIs were performed in the USA in 2013, and the IVIs number is estimated to rise further to approximately 5.9 million in 2016^[1]. Over the last decade, IVIs with anti-VEGF agents have exponentially increased in China, with an estimated 1.2 million injections in 2021 in Chinese mainland (unpublished data).

The dramatic increase in IVIs has been accompanied by an increase in evidence surrounding IVIs practice patterns and techniques. Several guidelines and consensus on IVIs

have been published in order to reduce possible risks and complications ranging from discomfort to severe complications, such as endophthalmitis, rhegmatogenous retinal detachment, and cataract formation^[2-5]. Despite the publications of these evidence-based guidelines, the practice patterns of IVIs still vary from practice to practice and from country to country.

It is unclear how these guidelines are incorporated in the real-world clinical practice in China. Differences in IVIs practice patterns may exist in several aspects such as procedure settings (operating room versus office-based), prophylactic antibiotics, use of mask and gloves, bilateral injections, *etc.* between Chinese ophthalmologists and retinal specialists from other countries. This study aims to describe the results of an online survey on IVIs practice patterns of ophthalmologists in China.

SUBJECTS AND METHODS

Ethical Approval The survey was conducted among the ophthalmologists, predominantly involving the retina specialists, from the member pool of a hospital-based national network, named “Brightness Center” (<http://www.brightnesscenter.com/>) constructed by National Clinical Research Center for Eye Diseases. Every participant has performed more than 100 IVIs previously. This study was certified by the Institutional Review Board of Shanghai General Hospital, Shanghai Jiao Tong University (Ethics approval No. 2022KY021) and permitted the administration of the web-based survey to ophthalmologists. This study adhered to the tenets of the Declaration of Helsinki. The informed consent was obtained from the subjects.

The questionnaire, including 24 questions on pre-injection, injection, and post-injection procedures, was prepared considering the current practice patterns and previous guidelines. The participants were contacted by the Brightness Center network to complete an anonymous, 24-question, internet-based survey. A link, directed to a web-based questionnaire page with secure confidential access, was sent to 657 ophthalmologists across China through the Brightness Center network website on February 13th, 2022 and three reminders were sent to participants who had not completed the survey by then. Participants were informed about the study goals and received instructions on how to fill in the survey and other details. Participants were masked from each other about their personal information and responses. Results were tabulated on February 25th, 2022.

RESULTS

A total of 333 participants (50.68% response rate) responded to the survey. The results of the survey of practices of Chinese ophthalmologists were shown in Table 1. The 86.79% (289/333) of the participants worked in Department of Ophthalmology in the tertiary general hospitals

(provincial or municipal medical centers), 3.6% (12/333) worked in Department of Ophthalmology in the second-class general hospitals (local medical centers), and 9.61% (32/333) worked in hospitals specialized in ocular diseases. Among the respondents, 57.36% (191/333) were retina specialists (including 41/333 medical retina specialists) and 42.64% (142/333) of the participants were multispecialty ophthalmologists focusing on both retinal and other ocular diseases such as glaucoma, cataract, *etc.* The 13.51% (45/333) of the participants were residents, 37.84% (126/333) were attending physicians, and 48.65% (162/333) were chief physicians. In terms of geographic distribution, physicians from 28 different provinces/municipalities/autonomous regions responded to this survey, including 25.83% (86/333) from the northeast of China, 37.24% (124/333) from the east of China, 20.72% (69/333) from the west of China, and 16.22% (54/333) from the central China area.

Pre-injection Practices In evaluating the systemic risk factors, 8.71% (29/333) of the participants routinely evaluated the cardiovascular and cerebrovascular risk factors by examining the patient’s medical history, and 91.29% (304/333) checked electrocardiogram (ECG) examination results and blood routine test results such as random or fasting blood glucose levels for their patients in combination with medical history evaluation. All participants ($n=333$) used prophylactic antibiotics, including 99.7% (332/333) who used topical prophylactic antibiotics, and 0.3% (1/333) who used systemic prophylactic antibiotics. The time period of topical prophylactic antibiotics usage was variable from 1d to 1wk, and the frequency varied from once to 14 times per day. The 99.1% of the responders (330/333) routinely monitored intraocular pressure (IOP) before injection, while 0.9% (3/330) did not routinely check the IOP. The 96.1% (320/333) of the responders routinely monitored blood pressure before injection, while 3.9% (13/333) did not routinely check the blood pressure.

Most (98.8%, 329/333) of the ophthalmologists performed the IVIs in an operating room only, whereas 1.2% (4/333) conducted the IVIs in an operating room, in a treatment room or in an office setting. Most of the respondents wore masks (99.7%, 332/333), sterile gloves (99.4%, 331/333) and sterile surgical gowns (96.1%, 320/333).

The 61.26% (204/333) of the respondents performed pupillary dilation before injection. Among the respondents, 97.9% (326/333) reported using topical anesthetics only, and 2.1% (7/333) reported using subconjunctival anesthetics only or in combination with topical anesthetics. The 95.8% (319/333) of the respondents applied povidone-iodine (PI) to the ocular surface before injection; others reported using Gentamicin or diluted Gentamicin before injection. Most respondents (58.6%,

Table 1 Practices of Chinese ophthalmologists

Questions and answers	No./total	%
Pre-injection procedures		
Systemic evaluation: medical history, ECG, blood test	304/333	91.29
Prophylactic antibiotics	333/333	100
Systemic prophylactic antibiotics	1/333	0.3
Topical prophylactic antibiotics	332/333	99.7
IOP check	330/333	99.1
Blood pressure check	320/333	96.1
Operating room setting	329/333	98.8
Mask	332/333	99.7
Sterile gloves	331/333	99.4
Sterile surgical clothing	320/333	96.1
Pupil dilation	204/333	61.26
Topical anesthetics only	326/333	97.9
Povidone-iodine application	319/333	95.8
Bilateral injection	170/333	51.05
Injection procedure		
Quadrant preference		
Superior temporal	135/333	40.54
Inferior temporal	91/333	27.33
Superior nasal	19/333	5.71
Inferior nasal	5/333	1.5
No preference	83/333	24.92
Needle gauge		
30	245/333	73.57
27	88/333	26.43
Measuring distance from limbus	326/333	97.9
Conjunctiva displacement	178/333	53.45
Post-injection procedures		
IOP check	108/333	32.43
Visual acuity check in the manner of HM/CF	293/333	87.99
Optic nerve perfusion observation	123/333	36.94
Topical antibiotics	333/333	100
Review patients on the following day	306/333	91.89

ECG: Electrocardiogram; IOP: Intraocular pressure; HM: Hand motion; CF: Counting fingers.

187/319) applied diluted PI (0.1%–0.5%) to the ocular surface or rinse the conjunctiva. Others (41.4%, 132/319) applied 5% PI to the intended injection site. About half of the respondents (51.05%, 170/333) performed bilateral injections in the same setting.

Injection Techniques As to the site of injection, 40.54% (135/333) of the respondents favored superotemporal quadrant; 27.33% (91/333) favored inferotemporal quadrant; 5.71% (19/333) favored superonasal quadrant; 1.5% (5/333) favored inferonasal quadrant, and 24.92% (83/333) reported no preference in terms of injection site. A majority of the study respondents (97.9%, 326/333) used calipers to measure the site of the injection from the limbus to ensure an injection through the pars plana; very few respondents (2.1%, 7/333)

didn't measure the distance. The 53.45% (178/333) of the respondents reported performing conjunctiva displacement prior to injection. The 73.57% (245/333) of the respondents reported using a 30-gauge needle for IVIs, whereas 26.43% (88/333) used a 27-gauge needle for injections.

Post-injection Care The 32.43% (108/333) of the respondents reported that they routinely checked IOP after injections. The IOP was checked at different time point from 30min to 24h after injections. Most of the responders (44/108) checked the IOP 2h after injections. A majority of the respondents (87.99%, 293/333) checked visual acuity in the manner of hand movements or counting fingers immediately after injection. More than one third of the respondents (36.94%, 123/333) observed optic nerve perfusion after injection. All

respondents ($n=333$) used topical antibiotics post-injection. The 57.83% (192/332) of the respondents used post-injection topical antibiotics for a week and 91.89% (306/333) of the respondents admitted to reviewing patient conditions on the following day.

DISCUSSION

The number of IVIs has increased dramatically worldwide over the past decade, and intravitreal delivery of therapeutic drugs has been considered the most effective treatment option for various retinal and choroidal diseases with reduced incidence of systemic adverse events. Several expert consensus recommendations and guidelines on IVI techniques have been proposed and updated based on evidence-based data or expert panel deliberations^[2-5]. However, a great diversity of IVIs practice patterns exists worldwide. Surveys of IVI techniques among retinal specialists have been conducted in the USA, Europe, India, the United Kingdom, Canada, Brazil, Turkey, Israel, and Mexico^[4,6-14]. To our knowledge, this is the first survey focusing on practice patterns of IVIs in China.

Endophthalmitis is the most devastating ocular complication following IVIs^[15-16]. According to a large Meta-analysis, the overall rate of endophthalmitis among patients receiving intravitreal anti-VEGF injections was 0.06% (197 of 350 535 injections) in the USA^[17]. Chen *et al*^[18] reported the rate of presumed endophthalmitis was 0.0079% (3 of 37 830 injections) using a standardized sterile technique in an operation room with prophylactic antibiotics for 3d pre-injection, topical 5% PI rinsing before injection, and post-injection prophylactic antibiotics for 3d in China. Despite the lack of evidence to support the routine use of pre, peri- or post-injection antibiotics to reduce the incidence of endophthalmitis^[19-21], topical prophylactic antibiotics are routinely used in China. All respondents in this study used prophylactic antibiotics both pre- and post-injection for several days. Surveys from the USA^[22] and Canada^[13] showed that pre-injection prophylactic antibiotics rate was 21% and 20%, and post-injection antibiotics rate was 28% and 29% respectively, which was much lower compared to our results. A major distinguishing feature of IVIs from other ocular invasive procedures is that most patients need repeated injections to the same eye. Frequent and repeated use of topical antibiotics following IVIs may lead to higher rate of antibiotic-resistance among conjunctival flora^[23-26]. The composition of the ocular surface microbiota may also significantly change when the patients received repeated perioperative local antibiotic eye drops, which may deeply influence the homeostasis of ocular surface^[27]. More education of ophthalmologists is needed to avoid the inappropriate use of topical antibiotics in IVIs.

IVIs are predominantly performed in the operating room in China, but these procedures are mainly administered in an

office setting in the USA and Canada due to limited availability of the operating room and high volume of injections^[13,22]. Li *et al*^[28] reported that rate of endophthalmitis following anti-VEGF IVIs was low whether the procedure was performed in the office or operating room. More than 95% of the respondents reported wearing gloves, masks and surgical gowns in our survey, which is much higher than in the USA and Canada^[13,22]. The use of gloves, sterile or nonsterile, has not been proved to reduce the risk of endophthalmitis, and should be combined with handwashing before and after patient contact. Physicians' wearing masks or minimizing talking during the IVI administration can prevent the spread of aerosolized droplets from the physicians and lead to a significant decrease in bacterial contamination and infection risk^[29-32].

In our survey, the rate of antisepsis with PI (95.8%) is lower than in the USA, Canada, and Mexico, where the rate is 100%^[12-13,22]. The rest 4.2% reported using antibiotics (Gentamicin) for antisepsis. Based on its broad-spectrum microbicidal activity, no resistance and a fast "kill time", PI has been recommended as the standard procedure for preoperative skin and ocular surface preparation^[2-5]. Topical 5% PI with a 30-second exposure time causes a significant reduction in conjunctival bacterial colonies^[33]. In our survey, some responders applied 5% PI to the ocular surface for 30–60s, and others rinsed the conjunctiva with 0.1%–0.5% diluted PI. *In vitro*, PI solution kills bacteria quickly at dilute concentrations (0.05%–1.0%). In many instances, PI kills bacteria more quickly at these dilute concentrations than conventional (5%–10%) concentrations. This is due to greater availability of diatomic free iodine (the bactericidal component of PI) in dilute solution. At high concentrations of PI, free iodine can be replenished easily from the surrounding iodine reservoir, while at low concentrations it must be reconstituted repeatedly to maintain its effect. In higher concentrations (2.5%–10%), PI requires 30–120s to kill bacteria, but a prolonged high bactericidal effect is maintained, thus it can be used as single application for eyelid and skin antisepsis, or as single instillation before IVI. On the other hand, PI in lower concentrations (0.1%–1.0%) needs only 15s to kill bacteria, but bactericidal activity duration is short, so it must be applied repeatedly in long-lasting intraocular operations. Current American IVI technique and monitoring guideline recommendations regarding PI application suggest using 5%–10% PI as the last agent applied to the intended site before injection^[2]. Differences in the ability to prevent endophthalmitis cases in IVI procedures between single application of 5%–10% PI and diluted PI still need further investigations.

Emphasis should be placed on antisepsis and aseptic technique among Chinese ophthalmologists, which plays the key role

in preventing endophthalmitis, rather than prophylactic antibiotics.

Our study does have some limitations. First, the response rate is not high (50.68%). However, these respondents are from 28 provinces/municipalities/autonomous regions in total, so the survey results could represent the real-world practice patterns in IVIs in most regions in mainland China. Second, selection bias, as in any survey, should be considered in assessing our results. Third, this survey didn't investigate the face mask wearing of patients during injection. Universal patient and physician masking has dramatically increased during the COVID-19 pandemic to decrease potential exposure to coronavirus, which is different from pre-pandemic practice pattern. Patient face masking during injections may result in increased aerosolized droplets dispersion toward the eye. Further studies are needed to elucidate the relationship between universal face masking and endophthalmitis rate.

In conclusion, this study provides a description of the real-world practice patterns in IVIs in China for the first time and offers critical information regarding education and training of ophthalmologists and amendment of local society guidelines.

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