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2018 Update on Intravitreal Injections: Euretina Expert Consensus Recommendations

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Keywords

Intravitreal injections · Vitreoretinal diseases · Treatment of retinal diseases

Abstract

Intravitreal injections (IVI) have become the most common intraocular procedure worldwide with increasing numbers every year. The article presents the most up-to-date review on IVI epidemiology and techniques. Unfortunately, important issues related to pre-, peri- and postinjection management lack randomized clinical trials for a final conclusion. Also, a great diversity of approaches exists worldwide. Therefore, expert consensus recommendations on IVI techniques are provided.

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Introduction

Already a century ago intravitreal injections (IVI) of air were used for retinal detachment repair [1]. However, it was only a decade ago, when Aiello et al. [2] published

the first consensus guidelines on “intravitreal injections.” Since then, IVI have become a cornerstone of ocular and in particular retinal care. It is reported, that over 4 million IVI were performed in the USA in 2013, rising further to an estimated 5.9 million injections in 2016 [3], highlighting the need for practical guidelines based on the latest evidence in order to reduce possible risks and complications ranging from discomfort to severe complications, e.g. endophthalmitis (EO) or retinal detachment.

A thorough assessment of IVI using the health care failure modes and effects analysis methodology reported 28 failure modes associated with the greatest clinical risk. The most hazardous were related to: room, equipment, and drug preparation; room, equipment, patient and surgeon sterility; injection technique and patient information [4].

This article is intended to highlight important aspects of pre- and postinjection management by examining the recent literature for evidence-based suggestions providing a standardized and structured approach.

Methods

Electronic searches including the following databases (Cochrane Library, Pubmed, Medline, Web of Science, Google Scholar) were performed between March 2016 and January 2017 for relevant articles published. Any study found was used to identify further relevant studies not found in the original search. Endnotes reference management software was used to manage citations. Database search results were imported, and care was taken to avoid duplication.

IVI Epidemiology

IVI have caused a huge revolution in the treatment of a variety of conditions, including age-related macular degeneration, diabetic macular edema, proliferative diabetic retinopathy, retinal vein occlusion, pathological myopia, uveitis, and many more. First introduced in 1911 as a way for retinal detachment repair by administering air inside the eye [1], IVI were subsequently (after 1945) used as a pathway for dispensing different drugs, in the treatment of EO, retinal detachments and cytomegalovirus retinitis [5–8]. In recent years, the use of IVI has reached an exponential growth, due to the progressive expansion of its clinical applications. Intravitreal delivery is currently considered the most validated treatment option for various retinal and choroidal disorders based on its ability to increase the ocular therapeutic effects of many agents, reducing the incidence of severe systemic adverse events [9]. From randomized clinical data to real-life evidence, the efficacy of IVI has been clearly documented, showing in many conditions not only a significant prevention from visual loss, but also maintaining or increasing visual acuity [10–13].

Thus, the proven efficacy of IVI of different agents compared to alternative therapies has resulted in millions of intravitreal procedures administered annually. Recent investigations show that the number of IVI has considerably increased worldwide. Between 1997 and 2001, less than 5,000 IVI were administered annually all over the world [14]. The global numbers went up significantly reaching 800,000 IVI in 2007 [14]. A more recent work showed that in 2009, in the USA more than 1 million IVI had been performed [15], and the numbers rose higher in 2013 (over 4 million IVI in the USA) peaking in an estimated 5.9 million IVI performed in the USA in 2016 [3].

Because of the relatively short half-life of intravitreally injected drugs, most patients are treated with a series of injections to obtain and maintain the desired therapeutic effects.

Considerations before Injection

Once the decision to perform an IVI is made and the administered drug is selected, the treating ophthalmologist must also take into account additional systemic and ocular conditions, which are not related to the indication of the IVI and may vary between patients and even in the same patient over time. In this section we will address these issues, which may affect the clinical judgment and influence the timing or technique of IVI.

Previous Episodes of Intraocular Pressure Spike after IVI

The volume expansion associated with IVI can cause an immediate rise in intraocular pressure (IOP), often called a “spike,” with IOP values over 30 mm Hg reported in as many as one third of procedures, 5 min after injection [16]. This typically resolves spontaneously within a few minutes, as the sclera expands to accommodate the change in volume. Yet, such episodes, especially if occurring repeatedly, can take a toll on the retinal nerve fibers [16–18]. The majority of IVI performed in clinical practice involve the delivery of 0.05 mL into the eye, but some cases involve the administration of 0.1 mL (such as intravitreal triamcinolone acetonide or ocriplasmin). The larger the injected volume, the greater the potential for an IOP spike. Additionally, rapid injection may also contribute to transient IOP elevation more than a slower injection into the eye.

The injecting ophthalmologist should be aware of IOP spikes possibly occurring after every injection.

Short-term increases in IOP are common immediately after IVI. Studies have shown that in most patients IOP returns to safe levels within 30 min after IVI [19–27]. It has been reported, that 89% of patients receiving intravitreal ranibizumab experienced an IOP rise of more than 30 mm Hg at 5 s after injection [23], approximately one third after the first 5 min [16]. In patients with a history of glaucoma or ocular hypertension the postinjection IOP decrease may be prolonged [20]. It has been observed that a sustained IOP increase occurred in 11% of preinjection normotensive eyes, which was controlled with topical medication [28, 29]. Yannuzzi et al. [30] speculate that using higher injection volumes as well as a rapid injection technique may both lead to sustained IOP elevation.

There is evidence that the healthy eye can withstand postoperative, transient IOP spikes without permanent damage. On the other hand IOP has to be rigorously controlled in patients vulnerable to vascular optic nerve damage, which are patients with glaucoma as well as patients

predisposed to anterior ischemic optic neuropathy [30] or branch/central retinal vein occlusion.

Studies showed that a combination of brimonidine 0.2% and timolol 0.5%, topical dorzolamide-timolol, performing ocular decompression with a mercury bag, or applying digital eye globe massage before the procedure significantly reduces IOP after IVI [31–34]. In contrast Frenkel et al. [35] concluded that the prophylactic use of IOP-lowering medication is ineffective in post-IVI IOP spike prevention. Particularly in diabetic patients, IVI-related ocular vascular events such as arterial or venous occlusion were noted in 2–19%, which was higher than compared to the general population [35]. It is suggested that an anterior chamber paracentesis should be performed in case of severe vision threat, if none of the before mentioned therapies is effective in lowering IOP [2].

It has been shown that smaller-gauge needles, typically used for IVI as they cause less pain, are also associated with less vitreous reflux and therefore a higher post-IVI IOP [17, 18]. A mild IOP elevation may go unnoticed, but a significant spike can be symptomatic, and associated with ocular pain, headache, and significant loss of vision (which may be reduced to finger counting or hand motion). The eye is firm, and an elevated IOP can be measured.

The majority of IOP spikes resolve spontaneously without intervention. However, several measures can be taken to address this complication. In the case of an acute IOP spike, which causes pain and loss of vision, a paracentesis should be performed in the anterior chamber, with release of some aqueous humor to relieve the pressure. It should be noted that performing a paracentesis may increase the risk of EO. If retreatment with IVI is considered later, digital massage of the eye prior to the injection is recommended, along with slower injection speed. It should be noted that digital ocular massage may elevate IOP, therefore it should be performed carefully.

In general the current literature shows that globe softening before IVI is not mandatory but can be considered in vulnerable eyes as for example in patients with glaucoma or patients with repeated IVI and known prolonged IOP spikes. In any event, monocular visual perception should be controlled by the treating physician immediately following the procedure.

Ocular Hypertension/Glaucoma

The injected volume used in clinical practice varies from 0.025 to 0.1 mL. Although the injected volume is only 1–2% at most of the total vitreous volume, it is a well-known fact that IVI can cause an immediate rise in IOP

as well as long-term elevated IOP. The elevated IOP is not merely the result of the added volume, but is also due to the properties of the injected drug. IOP elevation is associated with steroid therapy in general, and rates of this complication have been reported to be between 30 and 60% following IVI of triamcinolone acetonide [36–39], and between 30 and 50% following use of dexamethasone implants (Ozurdex) [40–43]. Anti-vascular endothelial growth factor (VEGF) agents have also been associated with elevated IOP, in as many as 12% of cases. Several mechanisms have been suggested for this adverse effect, including toxic changes, transient inflammation with production of cytokines that promote IOP elevation, and mechanical blockage of the trabecular meshwork [44–48].

In most cases, the IOP elevations are either transient or easy to control by topical treatments [16–18]. However, both short- and long-term IOP elevations are undesirable, especially in patients with prior glaucomatous damage. Therefore, the injecting ophthalmologist should always be aware of pre-existing ocular hypertension or glaucoma, and monitor IOP carefully. It is recommended that patients with pre-existing glaucoma should be under treatment and those with ocular hypertension should be monitored closely for signs of glaucomatous damage. Both patient populations should be followed for changes in IOP, as well as in their visual fields and optic disk appearance. These patients are potentially at greater risk for progressive worsening of their glaucoma due to repeated IOP spikes after IVI, and it is recommended that their IOP be monitored both after the IVI procedures and over time. Patients who do not have these conditions at baseline should also be monitored, as the IVI required for their treatment might constitute a risk factor for both ocular hypertension and glaucoma. If elevated IOP or other signs or symptoms of glaucoma are suspected, medical intervention should be undertaken. This will usually be initiating or adding a topical agent for IOP control.

It is important to note that any degree of pre-existing ocular hypertension or glaucoma does not constitute a contraindication for IVI [49]. As the ultimate goal is preservation of vision, these conditions should be managed. In patients who are steroid responders, an alternative agent should be used if possible to reduce the risk of IOP elevation. In all patients, close monitoring of the IOP is recommended, with a low threshold for initiating topical therapy and referring for additional testing or a glaucoma specialist if necessary.

Preexisting Ocular Conditions/Previous Ocular Surgeries

There is no preexisting ocular condition or surgery that constitutes a contraindication for IVI, as they can be safely performed 360° through the pars plana, allowing the injecting ophthalmologist some flexibility in choosing the exact site of the location. However, eyes filled with silicone oil can be very challenging, if IVI is necessary. These are rare cases and were not studied extensively.

Attention should be given to eyes with previous glaucoma surgery, such as trabeculectomy or a glaucoma drainage device, to avoid injection at the site of the filtering bleb or shunt. It is also recommended to avoid performing IVI close to a scleral patch in eyes that have it.

It has been shown that the pharmacokinetics of intravitreally injected drugs is different in previously vitrectomized eyes, with shorter half-life times and more rapid clearance. However, there is no change in IVI technique when performed on a previously vitrectomized eye. If the vitrectomy is recent, it is prudent to choose an injection location that is far from the sclerotomy sites.

Complex Medical or Ocular Conditions

In patients with coexisting complex medical and ocular conditions, care should be coordinated with their other physicians so the entire medical team is aware of all medical and ocular aspects [49]. No medical or ocular condition is an absolute contraindication for IVI, but in some cases they may affect the choice of drug used or the timing of the procedure.

Although no established guidelines on the safety of anti-VEGF agents have been established, we emphasize that the injecting ophthalmologist should be aware of the potential cardiovascular and cerebrovascular risks these agents may have. Caution should be exercised when IVI of an anti-VEGF agent is considered in patients with pre-existing cardiovascular or cerebrovascular conditions, especially if recent or unstable at the time of planned IVI. Consultation with additional relevant physicians is recommended prior to the administration. IVI of anti-VEGF therapy is not a medical emergency and can be deferred a few days to allow for multidisciplinary consultation to reduce the risk of any systemic complications.

Patients on Anticoagulation

No form of anticoagulation is considered a contraindication for IVI. Several studies have shown that anticoagulation was not associated with an increased risk of hemorrhagic or any other complication following IVI [50–52].

Active External Infection and Blepharitis

Currently only 1 published study addressed the issue of IVI in eyes with active external infection and blepharitis. In a prospective series of patients who developed EO after IVI compared with complication-free control cases, presence of blepharitis was found to be a significant risk factor for EO [53]. Eyes with active external infection likely had a higher than normal bacterial load, and it is possible that standard antiseptic techniques achieve sub-optimal results under these circumstances. Therefore, it is recommended that any active external infection including blepharitis should be treated prior to IVI [49, 53]. Patients who have chronic blepharitis even under permanent therapy can undergo IVI, but care should be taken to rinse the conjunctiva and fornices with povidone iodine (PI), to reduce the potential risk for EO. PI does not sterilize the conjunctiva and fornices but has been shown to be effective in reducing their bacterial load.

Pregnancy and Breastfeeding

Administration of any medicine in pregnant or breast-feeding women is always challenging, as for many drugs there is neither clear evidence for complete safety nor established guidelines for their use in these patients. The potential risks of treatment should be weighed against the possible consequences of deferring treatment, often in the absence of validated large-scale data. In contrast to their widespread use, there is a paucity of published information on IVI during pregnancy and breastfeeding, which consists of case reports and small series.

Both triamcinolone acetonide and Ozurdex have been reported to be used during pregnancy with no adverse effects [54, 55]. Use of anti-VEGF agents during pregnancy is more concerning, as the antiangiogenic effect may be hazardous to the placenta and developing fetus, especially in the early stages of pregnancy. There are several reports on the use of intravitreal bevacizumab during pregnancy, including the first trimester, describing no pregnancy complications and normal development after delivery [56–60]. However, its use has also been reported to result in loss of the pregnancy [61]. There is also 1 case report on intravitreal ranibizumab used safely in the third trimester [62], but no reports on intravitreal aflibercept during pregnancy.

One study reported undetectable levels of bevacizumab in the breastfeeding milk of nursing mothers who were treated with monthly injections after delivery [63]. There are no studies on the penetration of ranibizumab or aflibercept into breast milk. It should be noted that there are no studies on the potential effect of intravitreally in-

jected drugs during late stages of pregnancy on the long-term development of these children.

Considering the available information, we conclude that the risk-benefit ratio of intravitreal steroidal agents is acceptable during pregnancy if required. Use of anti-VEGF should be weighed against the possible risk of fetal developmental abnormalities or pregnancy loss, especially during the first trimester. Treatment should only be administered following a thorough discussion with the patient, as well as consultation with an obstetrician. Of the currently available anti-VEGF agents, ranibizumab may be the safest choice as it has been shown to have the most rapid clearance from systemic circulation and weakest effect on plasma VEGF levels [64]. Breastfeeding is likely not a contraindication to IVI therapy. It should be noted that these recommendations are based on sparse literature on this issue.

Peri- /Injection Management in Intravitreal Pharmacotherapy

Clinical Setting for IVI

Depending on the country where IVI are performed, national laws and regulations may apply regarding the clinical setting for injections. In the USA and Canada, IVI are mainly performed in the office [65, 66], whereas in other countries IVI are limited to the operation room or a sterile room with identical hygienic standards in order to decrease infection, especially EO.

A literature review shows that IVI-related EO rates are generally extremely low. Recently, a retrospective study of 5 US retina practices including over 500,000 IVI (bevacizumab, ranibizumab, aflibercept), all performed in an office-based setting, reported 183 cases of EO at a rate of 0.036% [67]. An evaluation of the prospective comparison of age-related macular degeneration treatment trials (CATT) data based on 18,509 injections performed in offices showed EO rates of approximately 0.06% [68]. Two further retrospective studies of 10,254 and 14,895 office-based IVI found similar EO rates of 0.029 and 0.057%, respectively [69, 70].

A recent retrospective analysis of 5,429 injections performed in the operating room (OR) exhibited an EO rate of 0.09% [71]. Another retrospective analysis including 40,011 IVI performed in the OR reported an EO rate of 0.007% [72]. Freiberg et al. [73] have recently reported the series of 134,701 IVI performed in an OR with laminar airflow, with a very low rate of EO of 0.0074% per injection.

A large French series (316,576 injections), in which 96% of injections were performed in a dedicated injection room and 40% had additional filtration airflow, reported a rate of 0.021%; the rate was not significantly different from injections performed without filtration airflow [74]. Smaller (approx. 40,000 injections) OR-based European series reported rates of 0% [75] and 0.0075% [76]. Similarly, a smaller German OR-based series (20,179 injections) reported a rate of 0.03%, although the cohort of patients injected later in the study had a rate of 0.009%, perhaps suggesting a learning curve effect [77].

A consecutive case series including a total of 11,710 IVI and comparing office-based (8,647) and OR (3,063) settings reported no significant difference in EO rates (0.035 and 0.065%, respectively) [78]. This has also been confirmed by a literature review summarizing data of 445,503 IVI, which did not show a significant difference between OR [71, 72, 78, 79] and office-based IVI [67–70].

The recent literature confirms that office-based and in particular OR-based injections have very low EO incidence. Although a few studies reported very low EO rates in OR-based settings, this had however not been confirmed by other studies based on similar settings. Moreover, a few studies reported similar EO rates in office-based settings compared to OR settings. However, prospective randomized trials are lacking.

In conclusion, operating theater, adequate room or in-office settings are recommended for IVI.

Anesthetics

Various techniques for pre-IVI anesthesia have been studied, showing controversial results. In everyday routine, pre-IVI anesthesia protocols vary widely, with proparacaine or lidocaine drops (90%) being most frequently used in Canada for example, followed by topical lidocaine gel, topical pledget, and subconjunctival lidocaine injections [65].

Currently, although there is not enough data to recommend one pre-IVI anesthesia technique over another, topical anesthesia is recommended, as it is the least invasive approach. However, there are not enough data to recommend a specific substance.

Topical Antisepsis

Contamination of the injection site can be caused by e.g. displacement of pathogens resident on the conjunctiva and eyelids [80] or the treating physician's mucosa while speaking to the patient during the procedure [81]. Therefore, the ocular surface pathogen load has to be reduced during preprocedure antisepsis. Today, PI is wide-

ly considered the standard of care for preoperative skin and surface preparation, since it has broad-spectrum microbicidal activity (bacteria, viruses, spores), no reported resistance and a fast “kill time” [82, 83].

Interestingly, free iodine is not liberated readily from PI at high concentrations, and diluting the solution facilitates free iodine liberation [84]. The free iodine concentrations for 10, 1, 0.1 and 0.01% PI are 5, 13, 24, and 13 ppm, respectively. However, free iodine is quickly inactivated upon reaction with bacteria and organic matters. At high concentrations of PI, free iodine is replenished easily from the surrounding iodine reservoir, while at low concentrations it must be reconstituted repeatedly to maintain its effect. In concentrations between 2.5 and 10% PI requires 30–120 s to kill bacteria, but a prolonged high bactericidal effect is maintained, thus it can be used as single application for eyelid and skin antiseptics, or as single instillation before IVI. On the other hand, PI in concentrations between 0.1 and 1.0% needs only 15 s to kill bacteria, but microbial activity duration is short, and applications must be repeated [82].

There are no reports on anaphylaxis related to PI in ophthalmic use. Also, PI displaced into the vitreous during an IVI procedure does not cause harm to the eye [85, 86]. Rare adverse reactions to PI are commonly related to its irritant properties to the ocular surface [83]. Moreover, a recent review on frequently claimed “iodine allergy” shows it lacks a scientific basis and that omitted preoperative disinfection might result in increased patient risks [87].

A recent prospective, randomized study investigating the contact time (15, 30, 60 s) of 5% PI during 131 IVI showed that a 30-s PI exposure reduced the resident bacterial load significantly compared to 15 s only [88]. This is also confirmed in a laboratory study investigating the bactericidal activity of PI dilute preparations [82]. A prospective randomized double-blind study in 100 patients undergoing cataract surgery compared the bactericidal efficacy of 5 and 1% PI. The authors showed that 5% PI significantly decreased postirrigation cultures compared to 1% PI [89].

Depending on the guidelines followed [90, 91], there are different recommendations regarding irrigation and installation of 5% PI in the conjunctival sac. The evaluation of 200 conjunctival cultures before anterior segment surgery showed significantly fewer positive cultures when PI 5% was used as irrigation compared to instillation [92]. Also, the repeated application of PI was shown to be significantly more effective compared to a single instillation in a small case series [93].

Chlorhexidine gluconate (0.1%) is used as an alternative to PI. In a recent Australian study comprising 40,535 IVI, chlorhexidine was well tolerated, associated with a low rate of postinjection EO and allergic reaction [94]. Moreover, another recent retrospective case series of 4,322 IVI exclusively performed under chlorhexidine gluconate antiseptics presented an EO rate of 0.023% [95], which is comparable to EO rates using PI [67]. However, alcoholic chlorhexidine bears a potential toxic risk on the cornea, yet aqueous chlorhexidine is considered an alternative in patients with local irritation or allergy to PI components [96].

Disinfectants are classified into 3 levels based on the spectrum of microbicidal activity [97]. High-level disinfectants are used only for instrument sterilization. PI is ranked intermediate, while chlorhexidine is part of the low-level disinfectant group. PI in concentrations between 0.1 and 1.0% requires 15 s to exhibit a bactericidal effect, while chlorhexidine in concentrations between 0.05 and 0.5% is used for 5 min or longer to kill *Staphylococcus aureus* and *Escherichia coli*. They both act directly on membrane proteins of bacteria to exhibit their bactericidal effect. Finally, chlorhexidine exhibits a much narrower antimicrobial spectrum compared to PI [98].

In summary, topical administration of 5% PI over 30 s can be considered a safe approach for antiseptics preceding IVI. Chlorhexidine is a safe alternative for patients with local irritation due to PI.

Periocular Skin Disinfection

Regarding periocular lid scrubs with PI, Aiello et al. [99] stated that lid scrubs are not to be performed. It is suggested that periocular lid scrubs increase the conjunctival bacterial count by dislocation from the eyelid margin. Only the combination of perioperative broad-spectrum fluoroquinolone and lid scrubs reduced conjunctival colony-forming units.

A study investigating conjunctival cultures of 120 cataract patients after applying preoperative eyelid chlorhexidine alcohol wash and conjunctival chlorhexidine rinse could not show significantly reduced bacterial counts compared to conjunctival chlorhexidine rinse only [100].

Currently there are not enough data to support preoperative lid scrubs or wash; thus, it cannot be recommended as routine and standard practice.

Perioperative Antibiotics

In theory perioperative topical antibiotics should lower the bacterial load of eyelashes, lids and conjunctiva and therefore result in significantly lower EO rates after IVI or

surgical intervention. A 2013 Cochrane review by Gower et al. [101] evaluating the effects of perioperative antibiotic prophylaxis on EO rates after cataract surgery analyzed data of 4 randomized controlled trials including 100,876 adults and 131 EO cases. The heterogeneous modes of antibiotic use and delivery made a formal meta-analysis impossible. The authors concluded that “it is unlikely that additional clinical trials will be conducted to evaluate currently available prophylaxis,” which is due to the fact that randomized controlled trials would need huge sample sizes to show an effect, and recommended to “rely on current evidence to make informed decisions regarding prophylaxis choices” [101]. In a recent meta-analysis comprising 174,159 IVI, Benoist d’Azy et al. [102] concluded that the systematic approach clearly shows that antibioprophylaxis is not required in IVI. In 2004 Aiello et al. [99] already stated that, besides the lower number of bacteria cultured from eyes after the use of perioperative topical antibiotics, there is no direct evidence that topical antibiotics lower EO rates after IVI. In a revision of these guidelines the authors argued that there was insufficient evidence to support the routine use of pre-, peri-, or postinjection antibiotics to reduce the rate of EO [49]. In fact, large studies have shown that topical antibiotics may even increase the rate of EO. It was hypothesized that the repeated antibiotic exposure, promoting the development of resistant strains, may lead to this paradox finding [103, 104]. Thus, there is no evidence to consider perioperative antibiotics as a standard of care [104–106].

Further, it should be kept in mind that the widespread and frequent use of topical antibiotics promotes increasing resistance to antibiotic substances [107–109] and growth of pan-drug-resistant bacteria, as recently observed in the USA [110]. Growing resistance among ocular bacteria has been observed following overuse of systemic as well as topical antibiotics in the eye. For further information, see Grzybowski et al. [111] and Bremond-Gignac et al. [112].

In conclusion, perioperative antibiotics cannot be considered the standard of care, as there is no evidence of prophylactic effects with regard to EO when using perioperative antibiotics.

Pupil Dilation

Today, pupil dilation (PD) is part of many protocols of randomized controlled trials [2]. A survey among Canadian ophthalmologists showed that most doctors dilate the pupil before IVI (83%) [65]. In the UK 78% of treating physicians dilated before the administration of intravitreal triamcinolone.

Depending on the guidelines followed, some instruct PD [113], some recommend PD, or it is at the discretion of the person injecting [99, 114, 115], while others do not mention PD [116].

In Brazil 12% of ophthalmologists responding to a survey had experienced crystalline lens touch during IVI [117]. Considering the fact that PD allows good visualization of the eye lens, instant fundus and central vessel examination (e.g. closure or pulsation) immediately after injection, it can be considered before IVI, particularly if a higher injection volume (>0.1 mL) is planned.

Currently there is no concluding recommendation to dilate or not to dilate the pupil for IVI. At the discretion of the injecting personnel, PD might be advisable for beginners in order to be able to immediately examine the retinal vessel perfusion after IVI.

Lid Speculum

Involuntary lid closure during IVI can lead to needle contamination. A prospective, randomized and double-blind study investigating pegaptanib in 1,186 age-related macular degeneration patients reported increased EO rates if no lid retractor was used [118]. Another prospective randomized study of 131 eyes undergoing IVI showed that the sterile lid speculum did not induce a change in the conjunctival bacterial load as hypothesized by potential secretion or dislocation from meibomian glands [119]. Bhavsar et al. [120] report a protocol based on 3,838 IVI including topical PI only, use of a sterile lid speculum, and topical anesthetic, which lead to EO rates as low as 0.09%. Low EO rates and effective lid closure prevention were reported by 92% of personnel performing IVI responding to a US survey on the use of an eyelid speculum [121].

Also, other techniques were proposed for eyelid retraction during IVI, such as the bimanual retraction technique with a reported EO rate of 0.03% [122] offering increased patient comfort in a small prospective randomized crossover study compared to the use of a sterile lid speculum [123]. Further, the cotton tip applicator lid retraction technique [124], the use of a conjunctival mold [125] or a Desmarres lid retractor [126] were reported.

Independently of the patients’ comfort, there are currently limited prospective and randomized data on the use of alternative lid retraction techniques. Any effective way to avoid lid closure during the procedure is justified, as there are insufficient data to support the use of one specific technique.

Needle Gauge and Length

Choosing the right needle gauge and length is not only important for patient comfort, but also for a safe injection procedure and efficient outcome. Frequently used needle sizes range from 27 to 30 gauge, but also 31-gauge and up to 33-gauge needles are used for IVI with increasing patient acceptance [127, 128].

A study in porcine cadaverous eyes shows that needles routinely used for IVI have many structural irregularities and attached debris such as silicone oil [129, 130], potentially influencing IVI outcome. The study also confirmed smaller scleral holes and less structural damage with an increased needle gauge, independently of the injection technique used, such as the tunneled or perpendicular technique. This is of interest, since scleral damage may cause vitreous incarceration or intravitreal medication reflux. Pang et al. [17] showed that a higher gauge (32 G) led to less postinjection reflux, but higher IOP immediately after IVI.

There is no data on the ideal length of IVI needles. However, laboratory data show that the use of 30-gauge needles and a deep placement of the IVI may reduce reflux and vitreous incarceration [130]. Regarding EO risk after IVI, needle size does not seem to be a relevant factor [131]. Thirty-gauge or thinner needles are recommended for liquid injections [132], whereas larger needles should be used when necessary, as for example for Ozurdex® injections. Expert panel guidelines suggest using any needle length from 13 to 18 mm [2, 115].

Injection Location

There is general agreement between IVI guidelines that injections should be made through the pars plana, between 3.5 and 4 mm from the limbus [2, 132]. A more posterior injection site potentially increases the risk of retinal detachment, while a more anterior approach increases the risk of traumatic cataract formation or hemorrhage, if the ciliary body is pierced. Approximately half of the respondents (56%) of a US survey measure the distance from the limbus to the injection site. Most of the injecting physicians use calipers (66%), or tuberculin syringes (28%); 6% use another device [120].

There is no clear agreement on the exact location or quadrant for IVI [133]. Most guidelines or expert opinions leave the selection of the quadrant to the injecting physician, based on patient-specific considerations [49]. If patients receive repeated IVI, it is also recommended to avoid injection in presclerotomy areas and switch injection sites, in order to prevent cumulative vitreous incarceration and persisting scleral hole [132].

IVI can be safely performed 360° through the pars plana; however, patient-characteristics should be considered.

Feasibility of Bilateral Injections

A case-control study in patients in need of bilateral anti-VEGF treatment showed that the majority of patients preferred same-day bilateral injections [134]. Besides patient convenience when performing same-day IVI, also cost-effectiveness has been discussed recently [67]. According to a US survey 46% of the responding ophthalmologists performed bilateral IVI [120].

However, a thoughtful risk-benefit assessment is advised to avoid the potential complication of bilateral EO.

Considering the current literature, same-day bilateral IVI seems to be a common procedure. It is recommended to treat each eye sequentially, and not reusing equipment such as the lid speculum or gloves.

Gloves, Clothing and Draping

The WHO Guidelines on Hand Hygiene in Health Care state that hand hygiene and surgical gloves are required for surgical interventions in general [82].

Although there are no prospective randomized data on the use of sterile and nonsterile gloves or drape for IVI, it has recently been advocated by a retinal expert panel that the use of gloves, either sterile or nonsterile, is consistent with modern office practice, combined with the handwashing before and after patient contact [49]. Moreover, it was argued that sterile drape should be considered optional [49].

In summary, there is no significant evidence that the use of sterile gloves or drape reduces EO rates or adverse events, as prospective and randomized controlled trials are lacking. From the available data we conclude to consider gloves, sterile or nonsterile, appropriate for IVI; draping, however, may not be essential. Appropriate clothing depending on the IVI setting is advised.

Use of Facial Masks

To mask or not to mask is of special interest considering the results of a meta-analysis comprising data of 105,536 IVI reported in the literature between 2005 and 2009. Streptococcal isolates were approximately 3 times more frequent in EO after anti-VEGF IVI than after intraocular surgery [135, 136]. In healthy subjects streptococci are reported to account for up to 7% of the conjunctival flora. The most common isolate in untreated eyes is staphylococcus [137–139].

In an experimental IVI setting, investigating the bacterial dispersal associated with speech, it was found that

Table 1. Expert consensus recommendations on intravitreal injections (IVI)

Subject	Recommendations
Clinical setting for IVI	Operating theater, adequate room or in-office setting
Anesthetics	Topical anesthesia No recommendation for a specific substance or technique
Topical antisepsis	Topical administrations of 5% povidone-iodine over at least 30 s into the conjunctival sac. Chlorhexidine for patients with local irritation due to povidone-iodine
Perioperative antibiotics	Not recommended
Pupil dilation	No concluding recommendation, but it might be advisable for beginners in order to be able to immediately examine the retinal vessel perfusion after IVI
Globe softening	No recommendation Might be considered in vulnerable eyes
Lid speculum	Sterile speculum is recommended
Needle gauge and length	30-gauge or thinner needles are recommended for liquid injections whereas larger needles should be used when necessary
Injection location	Inject through the pars plana, between 3.5 and 4 mm from the limbus Switch injection sites if patients receive repeated IVI
Feasibility of bilateral injections	Handle each injection as separate procedure
Gloves/draping	Gloves are recommended Draping may not be essential
Use of facial masks	Face masks recommended

wearing face masks or remaining silent during the IVI procedure leads to a significantly decreased bacterial contamination on culture plates. Also, talking in a reclined position similar to the position of patients in a reclined ophthalmic exam chair leads to significantly more bacteria colonies on the culture plate [81], indicating that the patient himself might disperse bacteria towards the injection site. This finding was confirmed in an experimental study. Ten surgeons recited a 30-s standardized script with and without face mask, while blood agar plates were positioned 30 cm below their mouths. The study shows that the use of a face mask and silence, both significantly decreased the dispersion of bacteria [140].

Again, a more recent retrospective analysis of 11,710 IVI showed no significant difference in EO rates between office-based IVI (8,647), which were typically done without a face mask and no limitation on speaking, and IVI performed in the sterile setting of an operating room (3,063) [141]. In an editorial of 2011, Schimel et al. [142] concluded that an adequate decrease in bacterial dispersal would conceptionally require the nurse or technician do-

ing the preparation, the physician administering the IVI, and the patient to wear a face mask, which is linked to increased costs and a substantial practical burden.

Strategies to minimize oropharyngeal droplet transmission, possibly causing contamination of the sterile injection site, may include a zero-talking, sneezing, coughing policy as well as wearing surgical masks. A Canadian survey revealed that 71% of health care providers therefore use sterile masks for IVI [65].

In conclusion, current clinical practices include minimized physician/patient talking during IVI, wearing of surgical face masks, and using face masks for nurses, technicians and physicians. Based on the data presented face masks are recommended for IVI.

Conclusions

IVIs have become the most common intraocular procedure worldwide with increasing numbers every year. The article presents the most up-to-date review on IVI

epidemiology and techniques. Unfortunately, important issues related to pre-, peri- and postinjection management lack randomized clinical trials for a final conclusion. Also, a great diversity of approaches exists worldwide. Therefore, expert consensus recommendations on IVI techniques (Table 1) are provided.

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