MANAGEMENT OF INTRAVITREAL INJECTIONS

MANEJO DE LAS INYECCIONES INTRAVÍTREAS

GÓMEZ-ULLA F1,3, BASAURI E2,4, ARIAS L1,5, MARTÍNEZ-SANZ F1,6

ABSTRACT

Purpose: The intravitreal injection is a minimally invasive technique which has been proved to be an effective therapy in the management of numerous vitreoretinal diseases. Its use has been rapidly increased in the last few years due to new medications and indications. However, non-standardized performance of this procedure might cause severe complications, being of special concern intraocular infection.

The aim of this Guide is to give ophthalmologists, with the information we have up to date, the guidelines needed to make this procedure safe.

Methods: 1. Reviewing the literature regarding evidence published up to date.
2. Consulting with experienced surgeons their common practice in this technique.
3. Contrasting the information from this Guide with those guides published in other countries.

Results: Although there is no complete consensus regarding the intravitreal injection procedure technique, the recommendations in this Guide are, up to date from our point of view, the most appropriate to prevent complications, specially infection. Of most importance are antisepsis with povidone iodine, the

RESUMEN

Objetivo: La inyección intravítreo es una técnica mínimamente invasiva de demostrada eficacia en el tratamiento de numerosas enfermedades vitreoretinianas. Su uso, gracias a nuevas medicaciones e indicaciones, se ha generalizado en los últimos años. La práctica de esta técnica sin las precauciones adecuadas, puede causar complicaciones graves, en especial la infección.

La finalidad de esta Guía es difundir entre los oftalmólogos, con la información que tenemos actualmente, las guías necesarias para hacer esta técnica segura.

Método: 1. Una revisión bibliográfica de la evidencia científica publicada hasta la fecha.
2. Consulta de práctica clínica habitual entre especialistas con experiencia acreditada.
3. Contraste de nuestra información con las contenidas en las guías publicadas en otros países.

Resultado: Aunque no hay un consenso absoluto, las maniobras recomendadas en esta Guía parecen, hasta el día de la fecha, las más adecuadas para minimizar los riesgos de complicaciones, en espe-
use of sterile material and gloves and an adequate injection technique.

**Conclusions:** Large series published of intravitreal injections which took place in clinic settings applying a procedure technique as recomended in this Guide, presented a very low incidente of complications, specially endophthalmitis (**Arch Soc Esp Oftalmol** 2009; 84: 377-388).

**Key words:** Intravitreal injection, endophthalmitis, ant-VEGF, triamcinolone.

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**INTRODUCTION**

The first reference to the use of intravitreal injections (IVI) was made in 1911 by Ohm, who utilized it as a technique for introducing air in the eye for repairing retinal detachment (1).

After 1945 IVI were utilized as a pathway for administering drugs, introducing penicillin for treating endophthalmitis (2,3) continuing with the use of this procedure for treating retina detachments (4-7), endophthalmitis (8,9) and retinitis due to CMV (10,11).

In recent years we have seen an exponential growth of the use of IVI due to the expansion of its clinical applications, initially for the injection of triamcinolone acetonide for macular edema, retinal vascular alterations, intra-ocular inflammations, choroidal neovascularization (12-20) and later, with the development of anti-angiogenic drugs such as sodium pegaptanib (21-24), ranibizumab (25-27) and bevacizumab (28-32), for treating choroidal neovascularization and other pathologies (obstructions of the central retinal vein and branches, diabetic macular edema, proliferative diabetic retinopathy, cystic macular edema and neovascular glaucoma).

Although some of these drugs are not designed for intra-ocular use, this administration pathway is unanimously accepted due to its advantages vis-à-vis other pathways for treating certain ocular diseases.

We are applying these treatments to a high number of patients and it seems we will continue to do so until we find other pathways equally or more efficient for introducing drugs within the ocular globe. On the other hand, we are making repeated injections until we find the way to maintain the medication inside the eye or to prolong its therapeutic effect.

We must take into account that the risk of these treatments by means of IVI will depend not only on the efficacy of the injected medication but also on its risks (safety, tolerance and complications inherent to the drug). Different drugs exhibited different risks in different proportions.

To these we must add the risks involved in the procedure.

The most feared complication of this procedure due to its potentially devastating effects is endophthalmitis. However, if we take certain asepsis measures which must be protocolized, the risk is low.

Even though we lack studies comparing different prevention maneuvers, this guide will adhere to recommendations which are either demonstrated as useful for preventing infections in IVI or are considered to be universal asepsis measures applicable to this procedure.

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**RISKS OF INTRAVITREAL INFECTION**

In 2004, Jaeger et al published the most important review ever made about the risks of this procedure (33) totaling 14,866 intravitreal injections of antiviral agents (ganciclovir, cidofovir, fomivirsen), triamcinolone, anti-VEGF drugs, gas, TPA, and metotrexate.

Said publication describes different types of risks such as endophthalmitis (including cases of pseudoendophthalmitis) (0.3%), retinal detachment (0.9%), intra-ocular hemorrhage (1.3%),
cataracts (development or progression, 9.9%) (this percentage increases when the follow-up is longer), uveitis/iritis (6.3%), sustained high intraocular pressure (2.4%-38.3%); more rarely, low intraocular pressure, optic atrophy, traumatic cataracts and retinal vascular obstruction. Sustained high ocular pressure, uveitis and the appearance or progression of cataracts could be related to the drug utilized, as is the case with uveitis, ocular low pressure and retinal vascular obstruction (cidofovir and fomivirsen). Retinal detachment would be related to the underlying ocular pathology (CMV retinopathy and diabetic hemovitreous).

This study considers infectious endophthalmitis as the most important risk of the procedure, with a probability of 0.3% if we include the cases of pseudo-endophthalmitis and endophthalmitis with negative culture. The probability is reduced in 0.2% in cases of endophthalmitis with positive culture. The prevalence is of 0.1% if we exclude the cases of intravitreal triamcinolone injections.

In November 2005, the Ethical Committee of the Pacific Medical Centre in California (34) proposed a clinical questionnaire for collecting security data (available in the net) after the intravitreal injection of bevacizumab: «The International Intravitreal Bevacizumab Safety Survey».

Between November 2005 and June 2006, the survey collected data from 70 centers of 12 countries totaling 7113 injections in 5228 patients, from which the following conclusions were drawn:

In relation to the procedure, the following complications were described: Corneal abrasions (0.15%), damages to the lens (0.01%), endophthalmitis (0.014%), retinal detachment (0.04%) and subconjunctival hemorrhages (0.03%).

In relation to the drug the following adverse effects were communicated: inflammation (0.14%), cataract progression (0.01%), central retinal artery occlusion (0.01%), sub-retinal hemorrhage (0.06%) and pigmentary epithelial detachment (0.06%). At the systemic level, the survey found 0.21% of HTA cases, 0.01% of transient vascular accidents and also 0.01% of deep venous thrombosis.

In January 2008, Wu et al (35) published a retrospective and collaborative study of PACORES about the safety and complications of intravitreal injections of 1.25 mg or 2.5 mg of bevacizumab with a 12 month follow-up. They collected 4303 IVI in 1310 eyes of 1173 patients. They reported systemic complications in 1.5% of patients (0.59% increase of arterial pressure, 0.5% of cerebro-vascular accidents, 0.4% of heart attacks, 0.17% of iliac arterial aneurysms and 0.4% of demises), while the ocular complications included 0.16% of bacterial endophthalmitis, 0.16% of tractional retina detachments, 0.09% of uveitis, 0.02% of regmatogenous retinal detachments and 0.02% of vitreous hemorrhages).

In addition, in March 2008, Moshfeghi (36) published a revision of 19,830 intravitreal injections of anti-VEGF drugs made at the Bascom Palmer Eye Institute of Miami between January 2005 and November 2007, with the result of 0.015% of endophthalmitis. And in May that year, Pilli et al (37) published a revision of 10,254 intravitreal injections of anti-VEGF medication (406 of sodicum pegaptanib, 6,347 of ranibizumab and 3,501 of bevacizumab) which exhibited a suspected endophthalmitis prevalence of 0.029%.

In previous studies with intravitreal injection of anti-angiogenic drugs, the prevalence of endophthalmitis due to injections was between 0.1% and 0.2% (23, 38, 39).

A variety of studies exhibited a higher risk of infectious endophthalmitis with triamcinolone injections: between 0.1% (40), 0.2% (33), 0.87% (41) and 1.9% (42). To this we must add the cases of non-infectious endophthalmitis and pseudo-endophthalmitis due to triamcinolone crystals in the anterior chamber: Between 0.1% (33) and 0.8% (43, 44).

**THE NEED TO PROTOCOLIZE THE PROCEDURE**

It is well known that endophthalmitis is the most feared complication of this procedure due to its consequences. However, the risk is low if we take certain asepsis measures. For this reason we propose to apply measures which are either demonstrated as useful for preventing infections in intra-vitreous injections or are considered as universal asepsis guidelines applicable to this technique.
The multicentre, prospective and randomized studies of Pegaptanib (23) reported a significant reduction of infection prevalence after changing the IVI protocol. Eight of the 12 endophthalmitis cases occurred in the first year of the study and, after modifying the protocol, no further cases appeared. This allows us to consider that the injection technique is very important to prevent endophthalmitis.

Several IVI guides have been published. The first (mentioned above) was published in 2004 in the «Retina» Journal (45) after a meeting of experts. Both the German Ophthalmology Society in 2005 (46) and the British College of Ophthalmologists in 2006 (47), published their own recommendations for this procedure.

**REQUIREMENTS PRIOR TO THE INJECTION**

1. Explain to the patient:
   a) the purpose of the treatment
   b) the details of the procedure to allow him/her to relax
   c) the expectations and possible risks
   d) the possibility of repeated injections and the frequency thereof
   e) alternative treatments, if any
   f) criterion for utilizing a drug that is not approved for intra-ocular use or for another disease, if applicable.

2. Signature of an informed consent for the procedure after the patient has understood the above points.

3. Request for compassionate use of medication or, if applicable, application of the legislation in force when using a drug that is not approved for intra-ocular use.

**PROPHYLAXIS BEFORE THE INJECTION**

1. Treat first the external ocular infection

   The external ocular infection (including active blepharitis), palpebral or lachrymal, must be treated before carrying out the procedure.

   Eye surface bacteria are the most common source of microorganisms that cause post-surgery endophthalmitis. We must also consider that palpebral anomalies such as ectropion can constitute a risk of post-surgical endophthalmitis (48-51).

2. Utilization of all the sterile eyedrops

   It is recommended to use sterile eyedrops for pupil dilatation as well as for topical anesthesia because the contamination of multiple use ophthalmic eyedrops in ophthalmology practices is demonstrated (52).

**PLACE OF THE INJECTION AND PROPHYLAXIS DURING THE PROCEDURE**

1. Injection in the practice, a general consulting room or a surgical room

   There is no specific recommendation about the required place for performing the procedure, provided that the area is sufficiently comfortable for the patient as well as for the ophthalmologist and that it allows a sterile procedure (37, 45).

2. Use of sterile material

   For performing a sterile technique, universal precautions must be taken such as the use of sterile gloves and material by the surgeon. The latter include:
   – A sterile blepharostat (to avoid the content of the needle with eyelids and eyelashes).
   – A sterile gauge
   – A sterile needle of 30 or 32 G.
   – Sterile tweezers and cotton swabs.

3. Use of topical anesthesia

   Experience has shown that topical anesthetic eye drops enhance the patient comfort during the procedure. The use of subconjunctival anesthesia
can also be considered but this requires manipulation and the possible formation of a subconjunctival hemorrhage.

In what concerns lidocaine gel, a study made in 2005 report that it increases comfort for performing IVIs and causes less subconjunctival hemorrhage than the subconjunctival injection of anesthesia (53). However, another study published the same year referred the use of this gel as a possible infection risk factor subsequent to cataract surgery (54). In addition, the lidocaine gel could act as a barrier for the action of iodinated povidone on the ocular surface, limiting its bactericide action. Besides, the gel itself could be a source of contamination. For these reasons, we cannot recommend its use.

4. Reduction of bacterial flora in the ocular surface and eyelids

Use of 5% and 10% respectively of iodine povidone.

There are several ways to reduce the bacterial flora of the ocular surface, such as the use of iodinated povidone and palpebral hygiene associated to the use of topical antibiotic prior to the procedure and the sterile isolation of the surgical area:

a) the use of topical 5% iodinated povidone in the conjunctival sac (55) is the only method that has proved to reduce the risk of post-op endophthalmitis in a cataract surgery prospective study (56).

In contrast with the application of two drops of 5% iodinated povidone over the conjunctival sac, conjunctival washing with 10cc of the product is associated to a lower growth of bacterial culture in conjunctival samples taken during cataract surgery (57). It is not known whether this difference had some effect in the prevention of endophthalmitis.

It is recommended to carry out an external cleaning of the eyelids with 10% iodinated povidone and the conjunctiva with a 5% dilution of iodinated povidone (45, 55).

The risk of allergy to iodinated povidone is very low. It is recommended to carry out skin tests to confirm said allergy, which must not be confused with irritation (allergy to iodinated contrast not necessarily implies allergy to iodinated povidone).

b) there is no evidence that the use of topical antibiotic prior to the procedure reduces the risk of endophthalmitis.

There is a study that presents a synergic action between iodinated povidone and topical antibiotic for reducing the bacterial flora of the ocular surface (58, 59). Other studies prove how antibiotic eye drops applied to the conjunctiva produce a marked reduction of the bacterial flora on the ocular surface (60-62).

However, as noted above, there is no evidence that all these precautions effectively reduce the risk of post-surgical endophthalmitis.

On the other hand, Deramo et al (63) presented a series of 42 eyes in 42 patients with acute postsurgical endophthalmitis. All were treated with pre-op broad range antibiotic. This means that, even when antibiotics are utilized prior to the procedure, endophthalmitis can occur.

A further study shows how resistances appear against broad range antibiotics commonly utilized as prophylactics for intra-ocular surgery (64).

c) in our understanding, the use of a sterile surgical area is not strictly necessary because the simplicity and swiftness of the technique entail a low risk of contamination from the outside of the eye and surrounding areas.

5. Avoid excessive palpebral manipulation

Excessive palpebral manipulation has been described as a cause of increased bacterial flora in the conjunctiva (65). A blepharostat that excessively compresses the eyelids can produce the same effect. It is recommended to avoid both situations.

6. Paracentesis

It is recommended to avoid whenever possible the opening of a new pathway to the eye, such as performing a paracentesis (45).

7. Mask

There are no data in our literature to suggest that the use of a surgical mask by the surgeon
may have a prophylactic effect or that the absence thereof may increase the risk of infection in this procedure.

8. Post-injection topical broad range antibiotic

The intraocular injection opens a pathway for microorganisms to enter the subconjunctival space. Therefore, it is recommended to use a broad range topical antibiotic at the end of the procedure.

SEQUENCE OF THE PROCEDURE

1. Pupil dilatation for visualizing the ocular fundus

Even though it is not essential, we believe that pupil dilatation is advisable for an adequate visualization of the ocular fundus as well as for controlling the «venous pulse» and «paleness» of the papilla, in case an additional action is subsequently required.

2. Topical anesthesia with sterile eyedrops

Use lidocaine 2% in a sterile ampoule or anesthetic eyedrops (tetracaine) opened when beginning the procedure.

3. Cleansing with iodinated povidone

As commented above, it is recommended to use 10% iodinated povidone for the skin of the eyelids, the palpebral edge and eyelashes, and 5% of the same product for the conjunctival sac, allowing it to act for a few minutes.

4. Application of the blepharostat

We believe that the blepharostats which include a flange are more adequate because they produce a better separation of the eyelids while isolating the eye from the palpebral edge and the secretion of Meibomian glands.

5. Measurements of the adequate distance from the limbus towards the pars plana

Utilizing a compass or a similar tool, we measure the normal distance from the limbus towards the pars-plana, of 3.5 mm in aphakic or pseudophakic eyes and of 4 mm in phakic eyes.

6. Indicate the patient to position the eye

On our own or with the assistance of a helper to hold the head steady, we ask the patients to look upwards and to the opposite side of that of the injection, which must be applied frequently in the lower temporal quadrant.

Some authors recommend administering the injections in the lower quadrant as a way to prevent a possible Bells phenomenon during the procedure. They also recommend different places for injecting in subsequent procedures as well as avoiding three and nine o’clock due to the presence of ciliar arteries.

7. Mobilization of the conjunctiva at the point of injection with tweezers or a cotton swab

In order to prevent the coincidence of the conjunctival and scleral orifice, we displace the conjunctival a few millimeters with a sterile cotton swab, a pair of tweezers or with the same instrument utilized for measuring the infiltration point, with care to avoid a subconjunctival hemorrhage. Utmost care must be applied in anticoagulated patients.

8. Insertion of the needle

The injection needles should be inserted perpendicularly through the sclera with the point towards the centre of the ocular globe to avoid damaging the lens. Special care must be taken to avoid contaminating the needle due to contact. The product (0.05-0.1 ml according to the drug) must be injected gently to prevent a diffusion effect.
9. Gentle extraction of the needle

A sterile cotton swab or the same measurement instrument can be utilized to prevent reflux of the injected medication or the aqueous vitreous and subsequent bleeding.

10. Administration of broad range antibiotic eye drops

A broad range antibiotic shall be utilized, two drops after applying the infiltration, for a few days after the procedure. By way of example, we usually utilize ofloxacin or ciprofloxacin, two drops every eight hours between three and five days after the injection.

11. Exploration of light perception and vision objects

If necessary, assess the possibility of central retinal artery perfusion. This can be done with indirect ophthalmoscope or with a slit lamp and non contact lens.

POST-OP GUIDELINES

1. There are no studies comparing different follow-up strategies after the procedure.
2. If deemed necessary, measure the intra-ocular pressure within 30 minutes after the injection (preferably with a non-contact tonometer).
3. Even though its efficacy is not demonstrated and it could increase the risk of bacterial resistance, the use of a broad range topical antibiotic is recommended for the first days after the procedure, considering the entry pathway to the subconjunctival space created by the injection.
4. It is usually unnecessary to cover the eye and the patient can go home after a few minutes. The checkup visit will depend on the disease, the drug injected and the number of infiltrations. Accordingly, it should be determined on a case-by-case basis.
5. It is recommended to instruct the patient about the possible local and systemic adverse effects, as well as providing in writing a list of alarm symptoms which may require help or an urgent telephone call. The text must clearly outline the active principle of the drug that was injected. The patient should keep this paper for the entire duration of the ocular process.
6. Rules to be delivered in writing to the patient:
   a) the injected intravitreal drug (active principle and commercial name)
   b) the injected eye
   c) the dosage and name of the antibiotic eye drops to be applied
   d) Symptoms of alarm which require contacting an ophthalmologist:

   reduction of vision, ocular pain in the presence of light, reddening of the eye for reasons other than the injection, or ocular secretions. Particularly important is a significant vision loss, with ocular pain and reddening, which could be symptoms of endophthalmitis.

   The patient must be instructed to avoid rubbing the eyes and avoid any contact with liquid for three days.
   The patient must also comply with the medication as well as the post-op follow-up visits.
   e) Alarming symptoms which require getting in touch with a resident physician or going to an emergency service (particularly after the administration of anti-VEGF):

   Even though the possibility of severe complications affecting the rest of the body is very remote, the patient must get in touch with medical services in the case of abdominal pain associated to vomit and constipation, abnormal bleeding, chest pain, difficulties in speaking, significant headaches or a weakness in any limb. As soon as possible, the patient must report these occurrences to the ophthalmologist.
   f) Contact telephone number of the clinic in which the injection was performed and the name of the ophthalmologist that carried it out.
INTRAVITREAL INJECTION ALGORITHM

INTRAVITREAL INJECTION SEQUENCE

1. OCULAR EXAMINATION AND INFORMED CONSENT
2. FIRST TREAT EXTERNAL OCULAR INFECTION
3. CARRY OUT THE PROCEDURE IN THE PRACTICE, THE NURSING ROOM OR THE SURGERY
4. UTILIZATION OF STERILE EYEDROPS
5. DILATATION OF THE PUPIL
6. TOPICAL ANESTHESIA

USE OF IODINATED Povidone

- 100% FOR CLEANING THE SKIN/ EYELIDS AND PALPEBRAL EDGE
- 5% IN CONJUNCTIVAL SAC, ALLOWING IT TO ACT FOR THREE MINUTES

USE OF STERILE GLOVES AND MATERIALS

- BLEPHAROSTAT GAUGE
- 30G OR 32G NEEDLE
- TWEEZERS/SWABS

INSERTION OF THE BLEPHAROSTAT

- AVOID EXCESSIVE PALPEBRAL MANIPULATION
Intravitreous Injections

**MOVILIZATION OF CONJUNCTIVA AND 3.5 MEASUREMENT**

- Fix the patient’s gaze

**INJECTION WITH 30G OR 32G NEEDLE**

- Avoid needle contamination due to contact
- Needle tip towards the centre of the ocular globe
- Gentle injection of the product

**ADMINISTRATION OF TOPICAL ANTIBIOTIC**

- Broad range antibiotic eye drops

**CHECK THE RETINAL CENTRAL ARTERY**

- Confirmation of light perception or visualization of ocular fundus
REFERENCES


Intravitreal Injections


36. Moshfeghi AA. Rate of endophthalmitis after Anti-VEGF after intravitreal injection. Retina Today March/April 2008; 75-76.


60. Snyder-Perimutter L, Katz HR, Melia M. Effect of topical ciprofloxacin 0.3% and ofloxacin 0.3% on the reduction of bacterial flora on the human conjunctiva. J Cataract Refract Surg 2000; 26: 1620-1625.


