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Retinal Toxicity of Medical Devices Used during Vitreoretinal Surgery: A Critical Overview

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Abstract
Retinal toxicity/biocompatibility of medical devices in direct contact with the retina is an important subject for clinicians and scientists. As these effects are not very frequent, there is also a relative lack of information for many clinicians. The past has taught us multiple times that there is a significant safety problem associated with severe loss of vision in affected patients. In this review, we want to classify medical products that are used in the back of the eye, describe recent examples of toxicity, critically reflect on the regulations that exist and suggest improvements that can be done to ensure patient safety without hindering innovation. ***Methods:*** Critical review of the recent papers and personal experience of the authors in this issue. Medical devices used in the back of the eye and recent examples of toxicity are described, regulations that exist are critically reflected and improvements suggested that can ensure patient safety without hindering innovation. ***Results:*** There is clear evidence of toxicity after intraocular surgery in any category. Some cytotoxic indirect methods have failed in detecting this toxicity. Some ISO rules do not seem appropriate. Postmarketing safety is missing. There is little data on this issue. ***Conclusions:*** The absence of a clear regulation of the production, purification and evaluation of the toxic effects of the medical devices supposes the possibility that products are not sufficiently safe to obtain the CE mark.

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Introduction

Pars plana vitrectomy was first introduced by Machemer et al. [1, 2] for patients with very severe vitreoretinal pathologies. After years of technical refinement, the indications were widened for less severe pathologies and even elective cases such as membrane peeling as a possible treatment option for epiretinal membranes [3]. After further technical refinements [4, 5], vitrectomy has become the second most common surgery in ophthalmology now covering emergency and elective indications [3, 6]. During the surgical procedures, many factors that might harm the tissue are among others the use of excessive endoillumination [7], an irrigation solution with a different composition than the human vitreous [8], the suppression of blood flow [9], air infusion [10], drugs [11] and medical devices [12]. All these elements are in direct contact with the retina and can potentially affect the neuronal tissue. In the past, these influences were hard to distinguish from functional damages caused by the underlying retinal pathology that lead to the necessity for a vitrectomy. As vitreoretinal surgery has become more elective, reports about retinal toxicity of, e.g., medical devices have emerged [13–16].

The spotlight was set on this topic after 2013 when cases of acute intraocular toxicity were reported in several European countries with at least three different products after an uneventful vitreoretinal surgery: Meroctane® (Meran, Istanbul, Turkey), AlaOcta® (Alamedics GmbH and Co., Dornstadt, Germany) and BioOctane-Plus® (Biotech Vision Care Pvt. Ltd, Gandhinagar, Gujarat, India). After a health alert was declared by the Spanish Agency of Medicines and Medical Devices (AEMPS), an expert committee put together by the Spanish Vitreo Retinal Society (SERV) revised 117 reported cases after AlaOcta® use where an acute amaurosis or a very low postoperative visual acuity shortly after surgery occurred. Some cases showed acute retinal necrosis of variable extension during the first postoperative week, optic nerve atrophy 1 month after surgery and arterial and/or venous retinal vascular occlusion. These findings were associated with the use of abovementioned medical devices [17, 18] (Fig. 1). Interestingly, the pharmaceutical companies selling these products adhered to the European guidelines for toxicity testing, but some of the safety tests failed to identify the toxic medical devices although they were performed according to the requirements of the Health Agencies and International Organization for Standardization (ISO) norms [17, 19].

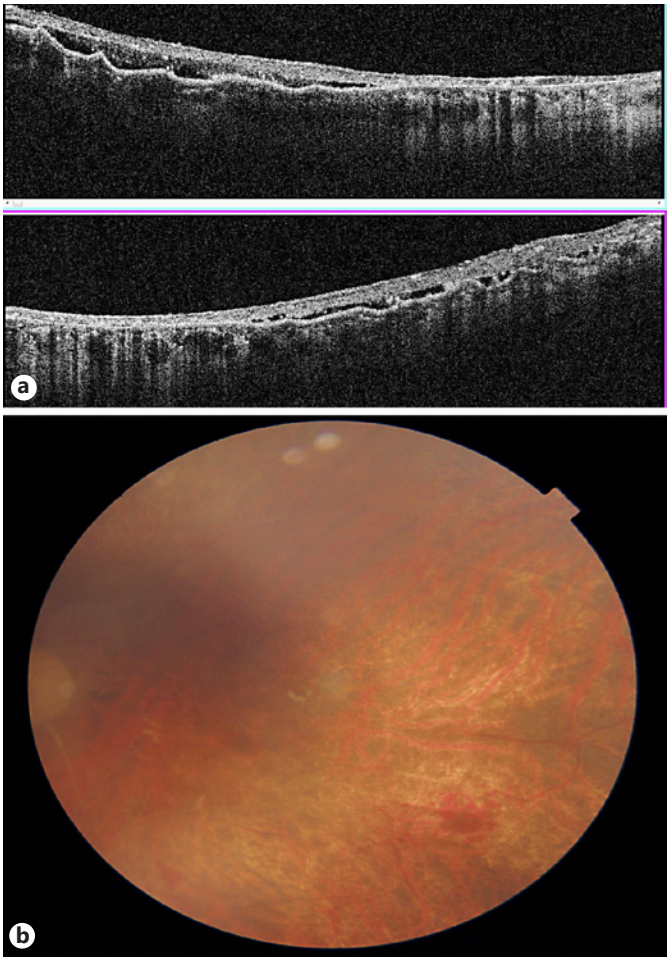

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Fig. 1. Clinical evolution of toxicity associated with the use of PFCL. **a** Optical coherence tomography showing retinal atrophy, wrinkling of the retinal pigment epithelium (RPE) and fluid between the RPE and neurosensory retina. **b** Fundus photography (50°) showing retinal atrophy, retinal hemorrhages, vascular occlusion and pale optic disc.

In this review article, we want to address specifically retinal toxicity of medical devices used during intraocular surgery, look at the weaknesses of existing regulations and introduce toxicity testing options in order to increase patient safety.

Medical devices that are used in the vitreous cavity in direct contact with retina can be classified by their time of possible interaction with the retina: (1) Ultrashort-acting medical products, such as vital dyes that are used once or repeatedly for 60 s to a few minutes and are removed afterwards. (2) Short-acting medical devices: intravitreal irrigation solutions are infused via a cannula and maintain mechanical stability during a vitrectomy (15 min up

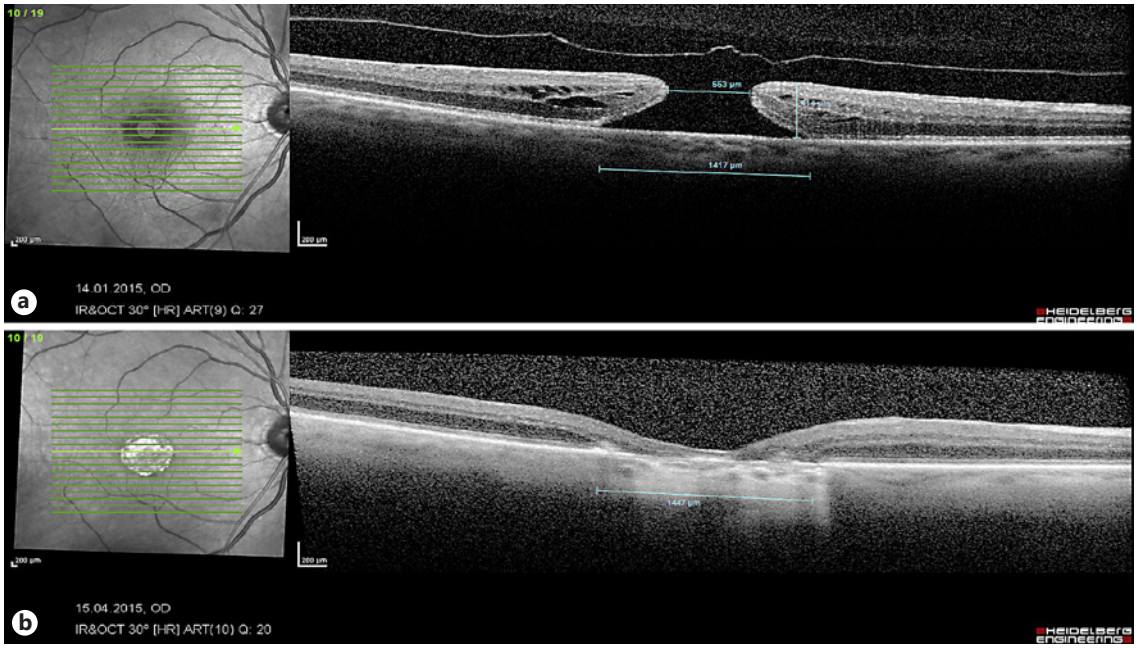

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Fig. 2. Clinical evolution of toxicity associated with the use of a vital dye. **a** Perioperative optical coherence tomography (OCT) showing a large macular hole with atrophic aspects and intraretinal pseudocysts. **b** OCT 3 months after surgery showing retinal pigment epithelium and photoreceptor atrophy.

to several hours). Heavy liquids (perfluorocarbon) are used to reattach the retina in cases of detachment (up to 1 h). (3) Long-acting medical devices: gases and silicone oil (SO) tamponades that remain inside the eye for a longer period of time.

1. Ultrashort-acting medical devices (≤60 s, repeated application): Vital dyes are used during retinal surgery to visualize anatomical structures such as epiretinal membranes. Indocyanine green (ICG) was the first ultrashort-acting medical device reported to induce toxic changes in the retina [20, 21]. The mechanism is not clear but some relationship to the solvent used is possible [22]. Another possibility is light-induced oxidative stress exerted by ICG [23]. Despite of these reports, ICG is still in clinical use (off-label) in the USA, because it is the only available option due to regulatory aspects. However, this might change in the future when other dyes will be FDA approved (NDA 209569, Brilliant Blue G Ophthalmic Solution, 0.025%).

Brilliant Blue G as a weak hydrophilic triarylmethane dye was introduced as an alternative; it is used commonly in Europe because it has a better biocompatibility than ICG [24–26] to stain specifically the inner limiting membrane (ILM) for ILM peeling. As a result of the technical refinement, mixed vital dyes that stain ILM as well as extracellular matrix and heavy vital dyes have been used. They yield easier intraoperative handling because of direct epimacular sedimentation and double staining in one application [20]. They have been shown to display favorable biocompatibility in ex-vivo models and a good clinical safety. However, different levels of impurities exist between different products, and labeling of impurities is insufficient for most products [16]. Labeling should at least be harmonized.

Recently, toxic effects of another dye acid violet 17 (AV 17) with 5% mannitol (AV17-M; Alapurple, Alamedics, Germany) have been reported (Fig. 2). While Gerding [27] pointed out that the existing data from ex vivo setups derived from lower concentrations than used in the final product, Hurst et al. [16] could show that there is a time-dependent negative effect of Alapurple® on ARPE 19 and on 661W cells in vitro. However, Röhrig's group investigated the clinical outcome in homogenous groups and could only show a negative trend of AV-17 compared to Membrane Blue Dual as the gold standard. They calculated that a sample size of 1,500 patients is necessary to investigate possible epiretinal toxicity of vital dyes in a clinical setting [28]. The mechanism is not clear

but could be attributed to a dose-dependent toxic effect [29].

2. Short-acting medical devices (≤2 h, repeated application): Perfluorocarbon liquids (PFCLs) can be used in cases of retinal detachment and are in direct contact with the retina for a variable, but usually short time (15–30 min, complex cases up to 60 min). They help to reattach the retina, reduce mechanical mobility during shaving and help to drain subretinal fluid. Sometimes they are used to refloat, relocate or stabilize an intraocular lens or lens fragments. PFCLs are removed during or at the end of surgery. They have an intermediate interfacial tension (IT) against water at 50 mN/m and a dynamic viscosity of 5.10 mPa·s [29]. As mentioned earlier, there have been reports of retinal toxicity associated with the use of different batches of PFCL products that left over 130 patients blind in several European countries. The investigations by the IOBA (Eye Institute of Valladolid's University, Spain) revealed that different batches of AlaOcta (Alamedics, Germany) showed different cytotoxic effects associated not only with the presence of OH derivatives but also other contaminants not directly related to the PFCL degree of fluorinization [17, 30]. These findings probably could be linked to other cases of severe vision loss in France, Switzerland, Germany and Saudi Arabia, without being officially reported. PFCL is considered to elicit inflammatory responses if left in the eye for longer periods of time and therefore should be removed completely at the end of surgery [31]. Retinal toxicity was formerly attributed to physical properties [13, 32] as well as toxicity and presence of impurities [33, 34]. It is important to mention that PFCL has been reported not to exert toxic effects as short-term tamponade (1–2 weeks) or even for long periods of time (although this is not recommended) [35].

Among all PFCLs, perfluoro-n-octane (PFO) has a high vapor pressure, allowing a more complete PFO removal during fluid-air exchange in an open system. Unfortunately, the PFO has also a high spreading coefficient that induces the PFO to dissolve into SO in small amounts. Despite an accurate removal of PFCL under air, small amounts of PFCL are still present in the vitreous cavity and can be responsible for inflammation and changes in SO rheological properties [36].

3. Long-acting medical devices (>30 days).

SO and Inflammation

SOs are used in complicated cases of retinal detachments. They stabilize the (surgically) reattached retina for a longer period of time and need to be removed in a consecutive procedure; buoyancy and superficial tension act as the main physical tamponading properties. Different SOs have different stabilities referring to the capability of SO to resist changes in its properties over time. Saccadic eye movements generate shear stress potentially able to overcome the IT, causing the breakdown of the originally inert bubble of SO into smaller droplets of SO, defined as emulsification; other factors are surfactants, heat, changes in pH level [37]. The scientific discussion on other risk factors is not conclusive yet [38].

Emulsification can be associated with retinal inflammation, toxicity and necrosis; a link between direct toxicity/immunogenicity and impurities/instability of the agent that modify the IT seems to exist [37]. The emulsified SO droplets induce a macrophagic foreign body reaction with phagocytosis of SO emulsion by retinal pigment epithelium cells, that can potentially lead to retinal necrosis [15, 39] and they have been also related to the development of glaucoma. One of the easiest ways to decrease emulsification is to increase extensional viscosity by increasing the length of the molecular chain of the compound. However, this also increases share viscosity (resistance in injection and removal of SO). Williams et al. [40] suggested adding 5–10% high-molecular-weight SO (423 kDa) to 1,000 cSt SO. The resulting SO has the same chemical properties of those used in clinical practice, but is more resistant to emulsification and is relatively easy to inject and remove [40, 41].

Surfactants

Surfactants are amphiphilic compounds that are able to lower the surface tension. They are low-molecular weight-components (LMWC) produced by the eye itself or are generated in the manufacturing process of SO. They contain both hydrophobic and hydrophilic groups, extending in both oil and water.

Biosurfactants are surface-active substances such as HDL-apolipoproteins, plasma lipoproteins, red blood cell membranes, growth factors and cytokines. They are mainly released by the retinal pigment epithelial cells or by the damaged blood-retinal barrier [37]. It was shown that the presence of albumin (at a concentration of 70 g/L, corresponding to the physiological serum content) remarkably affects the interfacial properties with an IT reduction of 70% [42].

The purification and ultrapurification of SO from short-chained siloxanes significantly decreases the amount of LMWC yielding concentrations of LMWC as low as 0.2–0.5 mg/kg. These compounds have demonstrated to be toxic [43]. Furthermore, even small quanti-

ties of detergents or cleaning substances from the sterilization processes of reusable equipment can increase the risk of emulsification in SO-filled eyes [44]. It is important to mention that this important information about purity cannot be found on the package insert of many medical devices.

Interaction between Heavy Liquid and SO

Sticky Oil Formation

Sticky oil is defined as SO-like material that remains glued to the retinal surface during SO removal [36] and was first described by Veckeneer et al. [36] in 28 eyes after direct PFCL and SO exchange using chromatography mass spectroscopy analysis in samples of sticky SO. Electron impact ionization mass spectrometry described that a small amount of PFCL dissolves into solution over time [45]. The incidence is higher with PFCL and heavy SOs [46]. The stickiness of the compound is related to a reduction in IT of the surrounding aqueous material contaminated with PFCL [36]. We believe that the defined sticky oil is not only "sticky," but is a "hyperviscous" compound produced by interaction between PFCL and SO [14].

The presence of PFCL induces changes in saturation points [14]. Solubility equilibrium is also temperature-dependent; therefore, also changes in temperature modify the saturation of heavy SO (HSO) by PFCL [14]. In the absence of PFCL, hyperviscous solutions have not been formed [14]. In surgical practice, the direct exchange of PFCL with HSO, and probably also the use of PFO, are not recommended during retinal surgery because of the direct contact between the two compounds at the oil interface and because of the high spreading coefficient.

Toxicity Tests

Before discussing the tests that are used to evaluate the cytotoxicity of medical devices, it is important to bear in mind that in the current classification [47], most of the products used during intraocular surgery are considered class IIa or IIb. This is a critical point per se, because if the Health Agencies understand that retinal tissue is similar to that of the central nervous system, the products would be considered class III.

Shortcomings of Present Tests

Current ISO Tests

For the detection of retinal toxicity, cell culture experiments may give first hints. In the recently mentioned example of PFO toxicity, all companies performed safety tests according to the ISO 10993-1 and ISO 16672. The ISO 10993 norms recommend several test methods to measure the toxicity which are categorized into extract, direct and indirect test method: 2009 "Evaluation and testing within a risk management process"; ISO 10993-5: 2009 "Test for in vitro cytotoxicity"; and ISO 10993-12: 2012 "Samples preparation and reference materials." More specifically, the ISO 10993 that sets the crucial guidelines for the biological evaluation of medical devices requires only testing the respective compound or its extraction products on specific immortalized murine fibroblast lines (BALB/c 3T3 and L929 cells) and on immortalized hamster pulmonary cells (V79).

Shortcomings

These cells lack the features of the much more delicate and sensitive differentiated retinal cells. Although fibroblasts could have an advantage to test cell damage compared to neurons because of their high rate of proliferation, they have some limitations due to their relative resistance to some toxic substances. Early signs of toxicity in animal models may be seen in Muller cells much earlier than neurons. The high metabolic state of certain cells (e.g., photoreceptors) in the neuroretina on the other hand may make them more susceptible to the hyperoxic state caused by the presence of PFCL or to other toxins.

For example Hurst et al. [16] could show that the retinal vital dye Acid Violet-17 had a negative impact on the viability of ARPE19 and 661W cells, while the ISO tests did not show this. If these experiments had been performed prior to market approval, no patient would have been harmed by this medical product. Moreover, the cytotoxicity tests that are required in ISO 10993 like MTT (colorimetric assay of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide to its insoluble/purple form formazan) or toluidine blue are quite crude and are unable to detect effects on apoptosis induction or other cellular responses that may be crucial for long-term effects. Furthermore, unlike fibroblasts, postnatal retinal neurons do not have the potential for regeneration.

Finally, the fact that a cell does not die when in intimate contact with a medical device does not guarantee that it maintains its function. For example after exposure to a stress factor (e.g., ischemia or a vital eye), a retinal ganglion cell may still be viable but be impaired in its conductive properties [48]. Thus, more retina-specific biocompatibility testing or even in-vivo testing should be required for the assessment of compounds or medical devices that are in intimate contact with the retina. But even

some of the animals that are proposed in the ISO for testing medical devices that are implanted for more than 24 h may not give sufficient preclinical information about safety. For example, several endotamponades appeared safe in the rabbit, but evoked pronounced inflammation or even retinal toxicity in human eyes. Later experiments with pigs showed similar results like in humans in one of these endotamponades [49].

Suggested Improvements

It is not the purpose of this review to propose guidelines at this point. A variety of groups (government officials, industry, basic researchers, clinicians…) are needed to improve the current situation. Generally speaking, the use of currently available products seems to be safe. However, the emphasis should be on extensive postmanufacturing chemical purity testing and on the traceability of the origin of the raw materials. Other options would be classifying retinal products as class III medical devices or drugs; however, this last option would lead to excessive costs and therefore less innovation without a clear benefit for the safety of patients.

General Suggestions

One alternative might be using primary retinal cells. However, they are hard to standardize in their composition, and their purity and quality are highly variable depending much upon the protocol, the experience and also the luck of the investigator. Immortalized retinal cell lines such as 661W cells (immortalized photoreceptors) or ARPE19 cells (human immortalized retinal pigment epithelium cell lines) may be more suitable for retinal toxicity investigations than murine fibroblasts [16].

Ultrashort-Acting Medical Devices

For medical devices that are removed within less than 24 h, no in vivo implantation data confirming safety have to be provided in order to get approval for human use by the respective legal bodies in the EU. Currently, not even testing on organotypic retinal cultures such as the isolated perfused retina or retinal whole mounts is performed routinely but could easily be implemented into the preclinical testing setup [12, 50]. It is obvious that neither the cell line and cell line species nor the method itself required by ISO 10993/EN30993 (L-929) reflects the clinical requirements. On the one hand, applying a vital dye in a cell culture for 60 s and then removing it, is a challenge in itself; on the other hand, simulation of longer exposition times would not meet clinical reality. The isolated retina would be a better option. Testing in animals is not a good alternative. Apart from significant anatomical and structural differences between most animal models and humans, standardization is difficult per se: ERG recordings vary with the depth of anesthesia and intraoperative complications, a standardized application of the dye epiretinally is almost impossible, because of vitreous remnants in animal models. The model of the isolated superfused retina is a standardized tool for toxicity testing and could be an appropriate method of choice for testing the safety of vital dyes [12].

Short-Acting and Long-Acting Medical Devices

Short-acting medical products such as irrigation solutions might also be tested using the isolated retina in a standardized fashion. SO might be a problem, because a direct epiretinal application would possibly hinder oxygenation by the nutrient solution and falsify results. Long-acting medical devices can only be tested for short-term toxicity in this set-up; therefore, animal models and cell cultures are the better options for preclinical safety analysis considering gases and SOs. WST-1 assay detecting cell viability and metabolic activity and the BrdU-Assay detecting proliferation are two of many options that can be used. The main problem seems to be the choice of cell cultures, e.g. recently RGC 5 was shown not to be of rat, but rather of mouse origin and, what is more important, not to be a ganglion cell line.

For the PFO liquid extract safety test, sample extracts are prepared by stirring the PFO liquids at 37 °C for 24 h in cell culture medium, and then exposed directly or indirectly to the mouse fibroblast cell cultures (L929 cell line). Also some other methods such as the agar overlay assay and filter diffusion test methods are used to expose the PFO liquids to mouse fibroblast cell cultures. However, none of these test methods provides a direct contact (which is happening in clinical practice) of the PFO liquids to cell culture and above all they have failed in detecting toxic lots. A new cytotoxicity test method developed by the IOBA of the University of Valladolid (Spanish patent No. 201630708 and International PCT No. ES2017/070365) aims at improving this shortcoming by directly exposing human retinal cell cultures (ARPE-19 cell line) and porcine neuroretina organotypic cultures to PFO liquids [17, 19]. This new test method has detected toxic lots of the PFO liquids which have previously been CE certified for safety but, unfortunately, had produced severe and acute clinical complications. These lots had different origins for fabrication, purification, and later on, had extract or indirect cytotoxicity tests for CE certification performed by different certified companies following the In-

ternational Standards for biological evaluation of medical devices (ISO). Therefore, ISO rules could be changed making direct tests mandatory. There are also some other critical factors that must be controlled before evaluating possible toxic effects, such as the duration of contact and maintenance of cultures [17, 19]. The importance of purity of the raw material, the purification process (e.g., two-step purification for SOs) and the quality management of the storage process are additional essential aspects.

Conclusion

Medical products are CE certified by the EU and have to undergo the ISO-recommended specific toxicity tests. European regulations for ultrashort-, short- and long-acting medical products in direct contact with the retina are insufficient to guarantee patient safety, because they do not reflect retinal toxicity and do not ensure purity of the product. Coordinated efforts must be made between researchers, clinicians, companies and health authorities to start a discussion about the class in which these products are currently located and the ISO standards that regulate the requirements of manufacturing, purification and biological safety control.

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