The Intravitreal Space of the Eye

Subjects: Anatomy & Morphology

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anatomy intravitreal drug delivery

1. Anatomy and Key Cells

The intravitreal space comprises the majority of the eye's volume and is located behind the lens of the eye [1]. The vitreous chamber of the eye is mostly filled with a gel-like solution called the vitreous body [1]. The vitreous body is 98.5–99.7% water containing salt soluble proteins and hyaluronic acid [1]. This is all contained by a gradient mesh of collagen that decreases in density towards the center of the structure [1]. The hyaluronic acid is located strategically within the collagen network to help maintain the spacing between fibrils and acts as a stabilizer [1]. The hyaluronic acid allows the gel to swell in the presence of water [2]. The water-bound hyaluronic acid allows the vitreous to maintain a gel-like consistency [1]. Hyalocytes, the phagocytic cells that comprise the vitreous body [1], are located in a single layer in the cortex of the vitreous and synthesize hyaluronic acid and glycoproteins. Hyalocytes also have binding receptors for IgG and complement components, which play a role in the immune response and in removing cellular debris [3]. Under certain pathologies, these cells can exhibit similar abilities to macrophages [1][4][5][6]. Their function is dictated by their location inside the vitreous [1]. In addition to hyalocytes, the intravitreal space contains a relatively small number of fibroblasts and macrophages. The fibroblasts are located near the front and back of the eye and are believed to produce collagen fibrils [1]. The macrophages are believed to originate from retinal blood vessels and only occasionally appear in the vitreous [1].

There are three density zones within the vitreous body. The vitreous cortex, also known as the hyaloid surface, is the most superficial zone [1]. It is composed of tightly packed collagen fibrils that run both parallel and perpendicular to the retinal surface [1]. This section runs from the side of the inner eye to the retina and contains several transvitreal channels [1]. The first transvitreal channel is the prepapillary hole, which is visible when the vitreous detaches from the retina, followed by the premacular hole, an area of lower density within the vitreous body. Finally, there are prevascular fissures, which exist where the collagen fibers enter the retina to attach to retinal vessels [1]. The next zone is the intermediate zone, which contains fine collagen fibers running anterior to posterior [1]. The fibers run parallel to the most proximal density zone [1]. This region also contains condensations of different collagen fiber densities, called vitreous tracts [1]. The final and deepest zone is Cloquet's canal, also known as the hyaloid channel or the retrolental tract. This zone is S-shaped and is a leftover of the hyaloid artery

system that was in its position during embryonic development [1]. This zone terminates at the area of Martegiani, a space at the optic nerve that extends forward into the vitreous in a funnel shape [1].

The vitreous chamber is predominantly surrounded by basal laminae, to which the vitreous attaches at several points. Its most notable connections are the vitreous base and the hyaloid capsular ligament of Weiger [1]. The vitreous base connects the vitreous to the basement membrane of the nonpigmented epithelium of the ciliary body and the internal limiting membrane of the peripheral retina [1]. For the retina, this is a continuation of the basement membrane of Müller cells [2]. The vitreous base connects the vitreous to the basement membrane and internal limiting membrane via vitreous fibers that are embedded into these membranes. The full base can extend a couple of millimeters into the vitreous [1]. The hyaloid capsular ligament, also referred to as the retrolental ligament, is an annular ligament located between the posterior surface of the lens and the vitreous. The potential space between these two surfaces is sometimes called the retrolental space of Berger. This ligament loses strength with age, particularly after age 35 in humans [1]. The vitreous is also connected to the macula via peripapillary adhesions around the edges of the optic disc. These adhesions also diminish with age [1]. In addition, fine collagen strands connect the vitreous to retinal blood vessels. These collagen strands pass through the internal limiting membrane to connect and surround the larger retinal vessels [1]. It is unclear how the vitreous attaches to the rest of the internal limiting membrane [1].

2. Interface

The intravitreal space is often used as a delivery site to treat eye diseases of the posterior segment. Techniques for administration of pharmaceuticals to the vitreous or to the posterior of the eye via the intravitreal space vary [7]. This section will explore some of the major approaches.

2.1. Injections

The first intravitreal injections (IVIs) were developed in 1895 to treat retinal detachment and vitreous hemorrhage [8]. However, since the 1970s, the number of IVIs has exploded, with antibiotics, steroids, gasses, and other compounds being injected once it became clear that IVIs could bypass the blood–retina barrier [8]. IVI is used as a method to achieve maximum drug concentrations in the vitreous and retina [7][9][10][11][12][13]. Under normal circumstances, the injection is accomplished using a 30–32 gauge filter needle, targeting the inferotemporal quadrant to avoid the visual axis [8]. It is believed that injecting more the 100 µL is unsafe, excluding gas-based treatments [8]. The needle is removed after injection, and a cotton-tipped applicator is placed over the injection site to reduce reflux for injections larger than 0.05 mL [8]. The use of antibiotics is a bit varied, with some groups preferring to skip their preoperative application [8]. Antibiotics help prevent complications such as endophthalmitis; however, there is some evidence of cases where antibiotics may not be needed [14][15]. The most common complications for IVIs are ocular pain, subconjunctival hemorrhage, and elevated intraocular pressure (IOP) [8]. They do also carry the risk of more severe conditions, such as subretinal hemorrhage, retinal toxicity, and retinal detachment, though these disorders are rare [8]. The most significant complication is endophthalmitis, with has a risk range of 0.14% to 0.87% per injection and occurs most commonly when antiviral agents are injected and least

commonly when gases are injected [8]. This is believed to be due to the increased frequency of injections needed for antivirals as compared to other compounds [16].

The administration of triamcinolone acetonide via IVI is currently a common treatment for a variety of ocular diseases. Although this method is generally accepted for use in appropriate circumstances, concerns have been reported surrounding potential complications to the vitreous. To further investigate, researchers at the Erciyes University Medical Faculty in Kayseri, Turkey, studied the effects of IVIs in 180 patients [17].

A total of 20 IVIs were administered to the 180 subjects (212 eyes), with 48 subjects' eyes receiving a second injection and 5 subjects receiving a third injection. Subjects were monitored for 4 weeks after injection via follow-up appointments. One of the most common side effects observed across the patient base was a transient increase in IOP, with the mean IOP spiking approximately 3 months post-injection and returning to preoperative levels (approximately 15 mm Hg) 9 months after the injections. IOP was observed to surpass 21 mm Hg in 44 of the tested eyes. In 14 of the tested eyes with diabetic macular edema, an intraocular lens implantation was required after the injections; however, 10 of these subjects showed previous signs of cataract development. The researchers determined that the continued use of triamcinolone acetonide injections to the vitreous is an effective treatment for appropriate ocular diseases; however, consistent monitoring for dangerous increases in IOP or the development of cataracts is a necessary precaution that needs to be taken when using such injections [17].

Similarly, to evaluate the risk of retinal detachment following IVI, Storey et al. evaluated 180,671 IVIs in 12,718 unique patients that received ranibizumab, bevacizumab, or aflibercept for neovascular age-related macular degeneration or retinal vein occlusion. They concluded that there was no association between the risk of retinal detachment following injection and diagnosis (p = 0.54), physician experience (p = 0.23), injection site (p = 0.41), caliper use (p = 0.75), or 31- versus 30-gauge needle use (p = 0.18). However, the macular status of the patient at the time of the retinal detachment did have a significant impact on the ultimate visual outcome. Ultimately, the rate of retinal detachment following a single IVI was 1 in 7500 [18].

2.2. Implants

Many of the drugs used to treat diseases of the posterior require repeated administration on a monthly or bimonthly basis, necessitating alternatives to the bolus IVI injection [19]. To further minimize complications and circumvent high clearance rates and the low bioavailability of common drugs, intravitreal implants have been sought after as an alternative [19][20]. These implants can be either biodegradable or semipermanent and are typically made up of a polymeric housing. Compound systems (nano- or microparticles or liposomes contained within a polymeric housing) are also frequently used [21]. In a study comparing the efficacy of a periocular triamcinolone acetonide injection, an intravitreal triamcinolone acetonide injection, and an intravitreal dexamethasone implant to deliver corticosteroids to treat uveitic macular edema, Thorne et al. concluded that the IVI and the intravitreal implant were superior to the posterior injection with a small increase in the risk of IOP elevation [22]. In a comprehensive, retroactive study of 6015 dexamethasone-containing intravitreal implants over an average of 18 months, cataract

progression and IOP rise were identified as the most common complications; however, intravitreal implants were considered generally safe with manageable risks [23].

Currently, intravitreal implants are used as an effective treatment for bacterial and viral infections of the vitreous and retina. Since the vitreous is a mostly acellular, heavily hydrated material, it serves as a very effective medium for drug delivery to adjacent parts of the eye. Drugs that are introduced to the vitreous also have less access to the systemic circulation, reducing the risk of nonocular side effects that can arise with treatments such as corticosteroids [24]. A wide range of drug products have seen use in both resorbable and semipermanent implants. Take, for example, the antiviral medication ganciclovir and its accompanying delivery device Vitrasert. Vitrasert is a product produced by Bausch + Lomb and was approved by the FDA in 1996 as a treatment for cytomegalovirus retinitis. Cytomegalovirus retinitis is commonly seen as a secondary infection brought on by the weakened immune system in AIDS patients; approximately 25–42% of patients diagnosed with AIDS will experience the infection [25]. Vitrasert is a polymer drug delivery system that can deliver ganciclovir at a steady rate for up to 5–8 months [25]. The device is composed of two polymers: an outer layer of drug-permeable polyvinyl alcohol (PVA), and an inner layer of impermeable ethylene vinyl acetate (EVA) [24][25][26]. The EVA layer partially encapsulates the inner payload of ganciclovir, effectively reducing the surface area through which the drug can diffuse into the outer polymer. The PVA serves to limit the rate of diffusion between the surrounding vitreous and the device as a whole. This limited rate of diffusion is a key factor in the stability of the device's release kinetics. The device can deliver a steady and reliable ganciclovir dose of 1 mcg/h without a large initial burst of the drug that can be problematic for the patient [26]. This particular implant is nonresorbable, so it must be removed from the patient's eye and replaced if the infection persists longer than the product's dose. Vitrasert is by no means a novel device in its market. There are several other devices operating in the same space, many of which are semipermanent polymer-based designs. While biodegradable alternatives do exist in the market, they are still less prevalent in clinical use and require more research to bring stable, consistent products.

Biodegradable sustained-release intravitreal implants are a particular focus of much research, as they offer the ability to deliver a steady supply of a drug to the vitreous or adjacent structures over an extended period but do not require a removal surgery. Liu et al. reported a composite poly(lactic-co-glycolic acid) (PLGA)-based microsphere loaded into a polyethylene glycol–poly(L-lactide) diacrylate (PEG-PLLA-DA) and N-isopropylacrylamide (NiPAAM) hydrogel.The microsphere-hydrogel composite system loaded with aflibercept was well tolerated, biocompatible, had biodegradable potential, and could treat CNV lesions for 6 months following intravitreal implantation in a rodent model. This device performed comparably to, if not better than, a bimonthly IVI injection and was advantageous in that it required only one treatment [27]. Varela-Fernández et al. described a poly-Ɛ-caprolactone (PCL) intravitreal implant loaded with idebenone for the treatment of Leber's hereditary optic neuropathy. This PCL delivery system was well tolerated, biocompatible, degradable, and able to release idebenone for over a year [28]. Systems such as these show much potential to overcome many of the shortcomings of traditional intravitreal drug delivery while providing many additional advantages, including targeted and sustained drug delivery, long-term sustained vitreous drug concentration, and a reduction in treatment frequency.

This entry is adapted from 10.3390/bioengineering9010041

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