ARTYKUŁ PRZEGLĄDOWY REVIEW ARTICLE
DOI: 10.24292/01.OT.300324.5

Clinical importance of proper regeneration of the ocular surface after cataract surgery

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HIGHLIGHTS

The basis of the treatment of eye surface disease occurring due to ophthalmic surgery are artificial tears. Artificial tears ingredients are hyaluronic acid and other substances, such as *Ginkgo biloba* extract.

ABSTRACT

Ophthalmic surgeries, including cataract surgery, lead to higher occurrence of eye surface disease. Tear film abnormalities are present in more than 60% of cataract patients. Patients with increased risk of perioperative dry eye syndrome should be treated before the surgery. Artificial tears are the first line treatment. In case they are insufficient, immunomodulants are used. Eyelid margin hygiene also exerts positive effect in patients with Meibomian gland dysfunction. Out of artificial tears ingredients, hyaluronic acid and *Ginkgo biloba* extract show positive effect.

Key words: cataract surgery, dry eye disease, Ginkgo biloba, hyaluronic acid, ocular surface disease, tear film

INTRODUCTION

Today, ophthalmic surgery is common, with an increasing number of individuals undergoing such procedures. According to estimates, 26% of the German population aged 70–74 years had undergone cataract surgery, with higher percentage in patients with diabetes and glaucoma [1]. Moreover, a significant number of people undergo refractive surgery (e.g., 7.5% of Koreans and 4% of Britons) [2, 3].

THE IMPACT OF OPHTHALMIC PROCEDURES ON THE PREVALENCE OF OCULAR SURFACE DISORDERS

The prevalence of anterior segment surgery has led to an increase in the number of patients presenting with ocular surface disorders, including dry eye syndrome (DES). The prevalence of DES symptoms following cataract surgery has been estimated to range from 9.8% to 34%, and increases with the age of patients. Peak severity of discomfort is observed 7 days after surgery [4, 5].

The etiology of DES symptoms following cataract surgery is multifactorial. During the procedure, small incisions are made in the cornea, which may disrupt the subepithelial plexus nerves responsible for the afferent pathways of tear secretion. It has been demonstrated that a reduction in nerve fiber density can be visualized using confocal microscopy after cataract surgery [6–8]. Corneal sensation is typically reduced three months after surgery due to changes in the morphology of nerve fibers, but it improves in the eighth month.

It has been demonstrated that local anesthetics and antiseptics (iodopovidone) used during cataract surgery are not indifferent to corneal and conjunctival surfaces. It has been demonstrated that topical preparations containing antibiotic and anti-inflammatory drugs commonly used in perioperative care contribute to problems with tear film secretion. Following phacoemulsification, a procedure used to remove cataracts, the number of conjunctival goblet cells, which are responsible for producing the mucous layer of the tear film, has been observed to decrease [10]. Furthermore, it has been demonstrated that cataract surgery is followed by metaplasia of epithelial cells in the inferior conjunctival fornix [10]. The aforementioned reports serve to highlight the significance of the toxic effects of topical preparations.

The procedure itself can result in ocular surface disorders due to corneal desiccation, abundant irrigation of the ocular surface (mechanical action of the liquid jet), and phototoxicity resulting from the adverse effects of light from the operating microscope [11].

TREATING AND PREVENTING DRY EYE SYNDROME AFTER CATARACT SURGERY

In accordance with the 2017 TFOS DEWS II definition DES is a multifactorial condition characterized by a lack of tear film homeostasis, in conjunction with associated symptoms resulting from tear film instability and hyperosmolarity, damage and inflammation within the ocular surface, and neurosensory abnormalities [12]. Dry eye syndrome is a prevalent condition, affecting approximately 6.8% of the American population and 34% of Japanese and Taiwanese residents [13].

Studies have shown that abnormalities in tear film break-up time (TBUT) and corneal fluorescein staining occur in 62.9% and 76.8% of patients referred for cataract surgery, respectively. Notably, as many as 69.8% of patients in the same group reported no subjective DES symptoms [14]. Consequently, expert recommendations indicate that patients should undergo evaluation for signs of osteoporosis prior to cataract surgery, with the implementation of appropriate preventive measures [4]. An essential component of the examination is the evaluation of the eyelid margins for meibomian gland dysfunction (MGD), which manifests as blocking the glands, swelling and redness, indicating inflammation of the eyelid margins. These signs are visible in the slit lamp, and can also be recorded with a meibography [12]. If MGD is diagnosed, it is advisable to start treatment when we prepare patient for the surgery [12]. This therapy consists of the following: hygiene of the eyelid margins with appropriate preparations, making warm compresses, and massaging the eyelid margin, and, in justified cases, using anti-inflammatory drugs [12]. In addition to MGD therapy, there are other procedures that can be implemented to prevent DES following surgery. For instance, it is the creation of a smaller corneal incision (or "microincision," defined as less than 2 mm), which helps reduce the degree of damage to the subepithelial nerves. Another procedure is the intraoperative use of epithelial protection (e.g., coating with a thick substance, such as viscoelastic), which prevents physical damage to the surface of the eyeball. Finally, the use of light filters in the microscope during surgery helps to prevent physical damage to the surface of the eyeball. Preventing intraoperative complications and not extending the procedure time beyond the norm reduces the time of potential corneal drying and toxicity on the corneal surface. Limiting the perioperative application time of drops and choosing preservative-free formulations exposes the cornea and conjunctiva to weaker toxic effects [11, 15, 16].

The treatment of DES resulting from cataract surgery is primarily based on topical preparations, namely artificial tear drops that are used routinely after ophthalmic surgeries, and should also be included when preparing patients with pre-existing tear film disorders for surgery. Among the active ingredients of moisturizing drops, hyaluronic acid

(HA) salts stand out as a particularly notable component, along with other active substances such as trehalose, dexpanthenol, hydroxypropyl cellulose, provitamin B_5, *Ginkgo biloba* extract, and others. Artificial tear preparations are designed to treat tear deficiency, reduce the concentration of pro-inflammatory cytokines in the tear film, and provide stability and adequate tear density through the presence of viscosity-enhancing ingredients and osmoprotectants. However, it is important to choose preservative-free formulations [4].

Hyaluronic acid

HA is an endogenous polymer of the human body. It is an unbranched compound belonging to the group of glycosaminoglycans (GAGs), which are components of the extracellular matrix. It is hydrophilic in nature [17]. The function of HA in the human body is contingent upon its location. At the cellular level, it is a component of the extracellular matrix, where intercellular interactions occur. In the skeletal system, it reduces friction in joints and participates in tissue repair processes. Moreover, the anti-inflammatory, immunomodulatory, antiproliferative, and effects on skin and tissue reconstruction properties of the compound are highlighted. It serves a passive structural molecule or as a signaling molecule. The physical properties of HA include hygroscopicity and viscoelasticity, which enable it to modulate tissue hydration and osmotic balance in the extracellular matrix [17].

In medicine, the properties of HA and its sodium salts are effective in promoting wound healing and regeneration, including ophthalmology. HA is naturally derived from the amniotic membrane and umbilical cord [18].

High molecular weight hyaluronic acid

In a natural state, HA can exist in two forms: a high-molecular weight hyaluronic acid (HMWHA) exceeding 1000 kDa (= 1 MDa) and a low-molecular weight hyaluronic acid (LMWHA) [17]. High-molecular weight hyaluronic acid (HMWHA) is a glycosaminoglycan found in tissues that has anti-inflammatory effects. Low-molecular weight hyaluronic acid (LMWHA), on the other hand, has the opposite effect, activating immune pathways. This occurs through the activation of macrophages, abnormal differentiation of dendritic cells, and the release of pro-inflammatory cytokines [18].

Furthermore, it has been demonstrated that as the molecular weight of HA increases, there is an enhancement in mucoadhesive properties in formulations applied to the ocular surface [19]. This translates into more efficient reepithelialization of the corneal epithelium, a significant reduction in inflammation and a longer moisturizing effect as a result of the higher molecular weight hyaluronate drops. Research on HMWHA has demonstrated its protective effect in eye drop form. The presence of HMWHA in the formulation of anti-glaucoma drops containing latanoprost has been shown to reduce the formation of inflammation and corneal surface loss compared to latanoprost alone, while maintaining the same hypotensive effect [20]. Preliminary studies have demonstrated that HA has a therapeutic effect at different doses, including 0.1%, 0.15%, and 0.3% [21]. Furthermore, results from a recent study suggest that HA at 0.15% is as effective in treating DES as the 0.05% cyclosporine formulation, with fewer side effects [22]. A form of HA with a high molecular weight of 1.1–1.7 MDa has recently been patented in the form of FHA 1.0®, a pharmaceutical-grade purity product. FHA 1.0® is used at a concentration of 0.15% and is a substance with a molecular weight of 1.1–1.7 MDa. The application of FHA 1.0® is to achieve multiple beneficial effects on the ocular surface such as moistening of the ocular surface, reduction of inflammation, and acceleration and enhancement of corneal re-epithelialization following cataract surgery.

Ginkgo biloba extract

Ginkgo biloba is one of the oldest tree species endemic to China, Japan and Korea [23]. It is referred to as a "living fossil" because its history has been traced back up to 280 million years [24, 25]. *Ginkgo biloba* extract is traditionally used in Chinese medicine. It has been shown to have therapeutic applications in numerous conditions, including the alleviation of neuropsychiatric disorders, dementia, and tinnitus [26–28]. *Ginkgo biloba* extract has been shown to prevent neurodegeneration and inhibit the release of inflammatory mediators in the nervous system [26]. Its potential mechanisms of action include increased blood flow, platelet activating factor antagonism, and prevention of membrane damage caused by free radicals [29]. However, in abnormal concentrations, *ginkgo biloba* extract can be toxic, and has been classified as a possible human carcinogen [30]. Furthermore, *ginkgo biloba* seeds in combination with ethanol may increase the risk of seizures [31].

Studies have indicated that *Ginkgo biloba* may be beneficial in the treatment of age-related macular degeneration (AMD) in patients who take the supplement orally, and that it may also protect retinal ganglion cells [29]. At the cellular level, ginkgo extract has been shown to exhibit antioxidant and apoptosis-inhibiting effects. It is not phototoxic [32].

The substance is effective in the treatment of eye surface diseases. Natural antioxidants, including *ginkgo biloba* extract, have been demonstrated to facilitate healing after chemical burns to the ocular surface and to enhance the antioxidant potential of tear film components [33]. In allergic conjunctivitis, the use of drops containing *ginkgo biloba* extract and HA has been shown to reduce conjunctival irritation and the amount of secretions in the conjunctival sac compared to the use of HA alone [34]. A prospective clinical study was

conducted to evaluate the effect of a formulation containing 0.15% HA and 0.05% *ginkgo biloba* extract following cataract surgery. The results of the study demonstrated that patients who used the eye drops exhibited less severe dry eye symptoms according to the Ocular Surface Disease Index (OSDI) questionnaire compared to patients who did not use the product. Additionally, tear break-up time (TBUT) was significantly longer in HA- and *Ginkgo biloba*-treated eyes. These differences were observed at 1- and 4-weeks following treatment. Furthermore, the study group exhibited a lower incidence of conjunctival injection 1 month after cataract surgery. The percentage of patients with corneal epithelial defects (CED) following surgery was between 10% and 60%, with the control group not receiving the drug exhibiting a higher percentage at 1–4 weeks after surgery. However, this difference was not statistically significant [35].

The author of the study, Professor Paolo Fogagnolo emphasizes the beneficial properties of *ginkgo biloba* extract, which enhances the normal secretion of tears and acts as an antioxidant, modulating inflammation and enhancing the regeneration of sensory nerve fibers. Consequently, *Ginkgo biloba* has been demonstrated to provide analgesic benefits in the context of postoperative pain [35].

CONCLUSIONS

The increasing prevalence of ophthalmic procedures and the implementation of rigorous perioperative care standards have led to a rise in the diagnosis of ocular surface disorders. It is therefore essential to ensure patient's comfort, optimize the results of the procedure, and facilitate rapid rehabilitation of vision. To achieve this, ocular surface should be properly regenerated. Among the preparations utilized perioperatively, HA eye drops are employed as a primary agent, as well as other eye drops containing excipients, including *ginkgo biloba* extract.

A clinical study conducted by Professor Paolo Fogagnolo has confirmed the efficacy of the formulation containing FHA 1.0® and *ginkgo biloba* extract. One of the advantages for the medical practitioner is that the use of eye drops enhances the efficacy of treatment by expediting the tissue regeneration. Additionally, it minimizes the probability of post-surgical complications such as DES. The product offers patients a number of benefits, including the alleviation of discomfort associated with corneal epithelial defects. Furthermore, a formulation containing HA and *ginkgo biloba* facilitates healing and ensures the optimal regeneration of the ocular surface.

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Authors' contributions:
Justyna Izdebska: concept of the manuscript, correction, content supervision; Katarzyna Samelska: literature review and data collection, writing the manuscript.

Conflict of interest:
The article was written in cooperation with Fidia Pharma.

Financial support:
The article was written in cooperation with Fidia Pharma.

Ethics:
The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.