Optometry: Open Access
ISSN: 2476-2075

Review Article Open Access

Human Serum Eye Drop Therapy: Regeneration of Corneal Layers by Stimulating the Cell Growth

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Abstract

Tears have antimicrobial, nourishing, mechanical, and optical properties. They contain components such as growth factors, fibronectin, and vitamins to support proliferation, migration, and differentiation of the corneal and conjunctival epithelium. A lack of these epitheliotrophic factors—for example, in dry eye, can result in severe ocular surface disorders such as persistent epithelial defects. Recently, the use of autologous serum in the form of eye drops has been reported as a new treatment for severe ocular surface disorders. Serum eye drops may be produced as an unpreserved blood preparation. They are by nature non-allergenic and their biomechanical and biochemical properties are similar to normal tears. In vitro cell culture experiments showed that corneal epithelial cell morphology and function are better maintained by serum than by pharmaceutical tear substitutes. Clinical cohort studies have reported its successful use for severe dry eyes and persistent epithelial defects. However, the protocols to prepare and use autologous serum eye drops varied considerably between the studies. As this can result in different biochemical properties protocol variations may also influence the epitheliotrophic effect of the product. Before the definitive role of serum eye drops in the management of severe ocular surface disease can be established in a large randomised controlled trial this has to be evaluated in more detail. In view of legislative restrictions and based upon the literature reviewed here a preliminary standard operating procedure for the manufacture of serum eye drops is proposed.

Introduction

Cornea is mostly composed of collagen and water and is enveloped by epithelium and endothelium. These layers cooperate to ensure tissue homeostasis by providing adequate corneal transparency and reliability. After injury, corneal epithelial cells regenerate and restore the physiologic tissue architecture. In addition, a concomitant nerve regrowth and a controlled neovascularization of the damaged surface may occur. Cellular loss needs replacement by cell growth and migration. The mechanism driving the epithelialization involves a multiplicity of cells stimulated by serum growth factors (GFs), mostly contained in platelet-α granules and issued by the same GFs into the blood during stress and tissue repair. The great quantity and accessibility of GFs and other signaling proteins in platelets with a consequent inhibition of cell apoptosis and improvement of cell proliferation, differentiation, and migration suggested the extensive use of platelet derivatives for clinical and surgical aims in regenerative medicine. Indeed, GFs, binding to tyrosine kinase or G protein-coupled receptor families, drive both the inflammatory process and the stroma remodeling through autocrine, juxtacrine, or, most commonly, paracrine means. Thus, the transcription of critical proteins for cell cycle returning to prewounding levels after the tissue healing occurs [1].

Toward this context, the lachrymal film plays a critical role such as resource of GFs. since the lack of tear epitheliotropic support promotes corneal opacity onset with consequent visual impairment. On the other hand, tear upregulation drives corneal epithelial hyperplasia, excessive deposition of extracellular matrix, and hypervascularization with cornea conjunctivalization. Here, we report the different concentrations of each GF in the human serum with respect to tears.

Failure of the corneal repair mechanisms leads to a chronic pathologic condition as persistent epithelial defects (PED) or dry eye syndrome (DES). PED result from several factors such as aging, chemical burns, systemic disorders, and drugs. Nevertheless, DES, associated to tear deficit or tear inefficiency, is able to promote the corneal epithelial instability and inflammation supporting PED syndrome. DES is caused by lacrimal gland imbalance often connected to systemic inflammatory diseases, such as Sjogren's syndrome, rheumatoid arthritis, diabetes, systemic lupus erythematosus, acne rosacea, and Graves' disease. In addition, hormonal modifications, drugs, and surgeries as well as the repeated use of contact lenses could be involved in DES development. On the basis of mechanistic criteria, International Dry Eye WorkShop has characterized two main subtypes of the disorder both interested by tear film instability and symptoms of discomfort [2]. Ocular dryness or irritation might increase light sensitivity, foreign body sensation, red eyes, poor vision, and daily life limitations which are the most referred symptoms which have great impact on patient quality of life. The best clinical marker for DES diagnosis and for the severity assessment is represented by the improved tear osmolarity. In addition, tear production is currently evaluated by Schirmer's testing, fluorescein clearance, and fluorescein tear break-up time (TBUT).

Up to now, there is no gold standard therapy for DES or PED. Current therapeutic strategies require the accurate identification of etiologic mechanisms that cause the corneal injury by providing epitheliotropic factors and enhancing tear replacement. When standard therapeutic options fail, the main treatment purpose is the increased patient comfort and corneal moisture through the instillation of artificial tears, corticosteroids, antibiotics, and use of bandage contact lenses [3]. However, natural tears have a particular composition of water, salts, hydrocarbons, proteins, and lipids that

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Received: 03-Mar-2023, Manuscript No: omoa-23-91611, **Editor assigned:** 06-Mar-2023, PreQC No: omoa-23-91611 (PQ), **Reviewed:** 20-Mar-2023, QC No: omoa-23-91611, **Revised:** 25-Mar-2023, Manuscript No: omoa-23-91611 (R) **Published:** 31-Mar-2023, DOI: 10.4172/2476-2075.1000189

Citation: Caitlin K (2023) Human Serum Eye Drop Therapy: Regeneration of Corneal Layers by Stimulating the Cell Growth. Optom Open Access 8: 189.

cannot be restored by pharmacological alternatives. Furthermore, artificial tear substitutes contain chemical preservatives associated with toxic and allergic reactions, especially for those patients with sensitive eyes. Moreover, the repeated instillation of topical corticosteroids could be associated with long-term side effects including cataracts and increased intraocular pressure.

A debated aspect of the treatment of corneal diseases is focused on the use of novel regenerative instruments for corneal regeneration. The evidence regarding the key role of several GFs for the integrity of the ocular surface fits the use of single recombinant GFs in several human corneal degenerative disorders. Nerve growth factor (NGF) alteration in corneal diseases has been largely evaluated; NGF pathway alteration has been tested in an animal model by demonstrating NGF to be involved in corneal healing and in sensory denervation. Moreover, in studies evaluating human being, low tears level of NGF has been proved to be reduced in eyes affected by dry eye and has been proved to be effective in several corneal diseases such as neurotrophic keratitis, immune corneal ulcer, and HSV keratitis and after cataract surgery [4]. Clinical trials are ongoing to evaluate therapy with NGF eye drops in corneal diseases and first results seem to be very promising.

In addition, a conditioned medium derived from human uterine cervical stem cells has been tested for corneal epithelial healing, and a therapeutically ocular surface medium, routinely used to culture epithelial cells, was suggested as novel eye drops for DES and PED.

Among these emerging therapies, the use of biologic eye drops derived from both human peripheral and umbilical cord blood serum plays a crucial role in several corneal diseases. Previous *in vitro* experiments showed that corneal epithelial cell morphology and cell functions are better maintained by human serum eye drops (SE) than pharmaceutical tear substitutes [5].

Here, we critically analyzed the current applications of SE in corneal diseases like DES and PED by focusing on crucial topics for its production and the current legislative restrictions in support of its use. To analyze the SE therapeutic achievement, we reported the most recent published randomized clinical trials (RTCs) and ongoing studies where this kind of treatment has been applied and compared to standard and other emergent treatments in severe ocular conditions.

Clinical applications and study results

Despite the fact that most of the authors found objective and subjective wellbeing after the treatment with SE, the comparison of clinical results is complex because data have been obtained from nonhomogeneous populations affected by several unrelated corneal diseases. In addition, the technical preparation of SE shows different dilutions obtained with different solutions, clotting phases, centrifugation forces, and time intervals, as well as different storage temperatures and times that can modify the final clinical outcomes and healing times.

Recent results have confirmed the efficacy of SE with respect to conventional therapy in patients with severe DES or PED both by improving tear film stability and providing subjective comfort. Moreover, two recent prospective interventional studies, on large cohorts of patients with PED treated with SE after ocular surgery, showed a significant or moderate improvement of delayed heal [6]. In particular, Chen et al. showed that 165 patients treated with 20% SE after penetrating keratoplasty drastically reduced postoperative PED when compared to patients that received artificial tears. In addition, Lekhanont et al. evaluated SE for PED in 181 patients showing a high proportion of complete corneal epithelialization in only 4 days with low rate of adverse reactions.

Case reports have been described about the use of SE in other corneal diseases like ocular graft versus host disease, bullous keratopathy, fulminant bilateral *Haemophilus influenzae* keratitis, neurotrophic corneal ulcer, anterior tissue necrosis after porous orbital implant, and Mooren's ulcer. In all these cases, SE allowed a complete corneal healing with an effective improvement of the clinical conditions.

Despite many promising results, some recent studies have questioned the validity of this treatment. A prospective cross-sectional study on 34 patients did not find that SE could be effective in secondary Sjogren's syndrome due to elevated serum proinflammatory cytokine levels. In conclusion, they advocated the need of recognized measures to define subjective symptoms and to assess the real effect of SE therapy for DES. The use of SE was compared in randomized trials to unconventional biologic therapies [7], which have gained a growing interest, such as umbilical cord blood serum (CBS) and amniotic membrane transplant. CBS is collected from umbilical vein after fetal delivery, manipulated, and collected similarly to peripheral serum. CBS is considered a reliable source of undifferentiated mesenchymal stem cells, which are self-renewal elements that are able to replace directly corneal keratocytes and conjunctival, limbal, and retinal nerve cells. In addition, CBS contains consistent levels of cytokines, GFs, fibronectin, prealbumin, and fatty oils that provide useful instruments for corneal differentiation. Moreover, CBS includes antibacterial agents as IgG, lysozyme, and complement but lower levels of vitamin A compared to peripheral serum. Despite the reduced immunogenicity of CBS with respect to peripheral serum due to the lower levels of IgM anti-A, anti-B, and IgG2, the use of the first is naturally associated to donor exposure and increased infectious risk and subjected to obstetric factors which could modify GF levels [8].

Some authors tested CBS for PED, DES, corneal diseases due to chemical burns, and surgeries associated. Due to prominent GFs, anti-inflammatory cytokines, and mesenchymal stem cell levels in CBS, some authors demonstrated the main effectiveness of CBS with respect to both conventional treatment and traditional SE in severe corneal diseases. For this reason, clinical ongoing trials are mostly focused on the comparative evaluation of the use of SE and CBS, especially in DES, PED, and ocular GVHD. In six ongoing studies reported on CBS eye drops, four are comparing CBS versus traditional SE and only one study analyzes amniotic membrane transplant versus SE in 180 patients with PED.

Future directions

Several fields of medicine are focusing on a regenerative approach to treat pathologic conditions affected by insensitivity and toxic reactions to standard therapies. In this context, tissue engineering and regenerative medicine are the present and the future aim of clinical therapy, especially where traditional treatments fail or promote severe adverse events.

A number of corneal conditions are often not fully managed by standard treatments and are characterized by intolerances and systemic effects. New treatments have to be considered. Subjective and objective results suggest that biologic therapies for corneal surface alterations like SE treatment could be an effective option. Indeed, the use of biologic eye drops provides the beneficial effects of vitamins, GFs, and cytokines by correcting delayed corneal healing pathways and by restoring balanced mechanisms [9].

However, the technical preparation of human serum for ocular instillation should require a well-equipped laboratory with specialized trained personnel as well as the respect of aseptic and quality procedures. In addition, methods for SE production including the proper additive and GF doses should be optimized according to well-established guidelines and standardized quality controlled protocols. Additionally, informed consent should be obtained from each patient in case of allogenic somministration to avoid ethical and juridical implications owing to blood transfusion practices and legislative restrictions should be carefully respected to minimize the immunological and infectious risks [10].

Conclusions

To date, clinical benefits of SE therapy have been demonstrated by some published studies. Most of the recent analyzed trials have tested the clinical results coming from SE treatment through the comparison with traditional therapeutic approaches such as artificial tears, antibiotics, or corticosteroids. Several randomized studies suggest that SE treatment leads to an improved tear film stability and subjective comfort by determining a faster epithelial healing time and a better corneal transparency without increase of vascularization or fibrosis. Moreover, several data have confirmed the safety and the almost absolute absence of toxic and side effects, especially in severe case of DES or in PED. On the other hand, the evaluation of the ongoing studies on this therapy showed that the newer fields of clinical research are focusing on alternatives to SE like CBS. In this regard, many studies are testing CBS and its therapeutic properties and safety. However, further studies with large populations comparing biological therapies with the traditional ones in corneal diseases are needed to provide the best treatment tailored to the singular patient.

Forthcoming conclusions will guide future efforts useful to clinical advances. They will clarify the therapeutic limits and resources of these emergent biologic therapies for corneal surface alterations, especially for refractory patients.

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