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REVIEW ARTICLE

Artificial tears to treat dry eye syndrome

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Abstract

Dry eye syndrome (DES) is caused by insufficient tear discharge, abnormal tear composition, or excessive evaporation of the tear film. It is a source of anxiety and discomfort. Treatment of DES is long-lasting and often unsatisfactory. Various treatment regimens are recommended based on the application of tear-imitating liquids produced by the pharmaceutical industry. The use of products approved for clinical use can however be limited by allergic reactions of some patients. In such cases it is recommended to use artificial autologous serum tears.

In some patients, blood collection is impeded and autologous tears cannot be processed. Other ways of obtaining artificial tears from material of human origin are therefore sought. Allogeneic preparations from blood donors are becoming more common. There is ongoing research into obtaining artificial tears with different techniques and from source material other than serum, namely platelet lysate and umbilical cord blood.

In Poland, there are no legal regulations regarding the preparation of artificial tears. The Institute of Hematology and Transfusion Medicine in Warsaw has been preparing autologous artificial tears from serum for over 40 years. Since 2019, research has explored the possibility of using allogeneic preparations.

Finding optimal treatment options for patients unable to use medicinal products, or for whom such products are ineffective, is a huge challenge worldwide. Efforts should be directed at developing the most uniform preparation methods and quality standards for each type of preparation. The growing number of publications on the subject shows the necessity of satisfying this need.

Key words: dry eye syndrome, autologous eye drops, allogenic eye drops

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Introduction

Dry eye syndrome (DES) is a condition caused by insufficient secretion, abnormal composition or excessive evaporation of the tear film which leads to injury and peeling of the eyeball epithelium. It may be attributed to endogenous cause and/or occur as result of physical, chemical or biological external factors. The condition is increasingly common [1].

One cause of DES is atrophy of the lacrimal gland as a result of abnormal immune responses or surgical intervention. The condition may also be attributed to damage to numerous lacrimal glands and reduced tear production. Among other causes are: Sjögren's syndrome, graft-versus-host disease (GvHD), sarcoidosis, infectious mononucleosis, acquired immunodeficiency syndrome (AIDS), and neurological conditions. DES may also be caused by dry, well-ventilated or air-conditioned rooms as well as dust, chemicals or smoke which irritate and dry out the eye.

Other causes may include lacrimal duct air (eyelid) regurgitation when the eyeball is not sufficiently moistened although tear production is normal. Another cause is incorrect composition of the mucus layer as a side effect of oral drug intake or topical drug application into the conjunctival

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sac. Bacterial infections inside the edge of the eyelid and conjunctiva may also be responsible for disorders in the fatty layer of the tear film.

DES troubles patients, causing physical as well as emotional discomfort. The most common symptoms include redness, itching, a feeling of burning and "sand under the eyelids" as well as the presence of a foreign body, increased mucus, watery eyes, photophobia and eye pain. Visual disturbances are reported, and images are blurry and out of focus. Some patients experience photosensitivity or ocular pressure.

Dry eye syndrome treatment

Unfortunately, the treatment is long-lasting and often unsatisfactory. Various treatment regimens are recommended based on the application of liquids imitating tears, i.e. artificial tears produced by the pharmaceutical industry [1].

Products approved for clinical use are safe, but their use however may be limited by allergy in some patients to substances in the drops, most often to preservatives. These may be responsible for local anaphylactic reactions. In such cases, it is recommended to use artificial serum tears.

Serum obtained from human blood consists mainly of water, and to a small extent of proteins, electrolytes, growth factors, vitamins, and other components secreted from platelets in the clotting process. Viscosity and composition ensure adequate moisturising of the eye epithelium, and the effect is maintained for a certain period of time. Artificial serum tears are a safe product. They contain no preservatives. Moreover, they help induce regeneration of damaged epithelium [2].

Worldwide, there is growing demand for artificial tears. In Australia for example, demand increased by 30% just between 2014 and 2015. Also, the number of publications on autologous preparations used to treat DES is steadily growing [3–5].

There is however, the problem of eligibility of patients for the procedures of collecting blood for artificial tears preparation. Indication for the use of artificial tears should be determined by an ophthalmologist and the patient referred to a special center where artificial tears are prepared according to procedures which guarantee the safety of both patient and product.

Autologous serum eye drops

In Poland, there are no legal regulations regarding the preparation of artificial tears. Other European countries follow recommendations of the Guide with regard to the quality and safety of tissues and cells for human application [6].

The first center in Poland to prepare artificial tears was the Institute of Hematology and Transfusion Medicine (IHTM) which started this activity in the late 1980s. Since then, IHTM staff have trained representatives from other entities, and currently several blood transfusion centers (CKiK) also provide this service. Of crucial importance is the fact that CKiK are well able to prepare sterile and safe artificial eye drops. Moreover, the activities of CKiK are subject to constant supervision by IHTM. Regrettably, there are increasing reports of offers of artificial tears from entities not subjected to any supervision; little is known about the conditions in which that product is prepared.

Selection of patients and their background

It is extremely important for the patient to be well prepared in order to obtain a high-quality product. In the case of autologous artificial tears, the patient should inform the physician responsible for the procedure of any medications that he or she takes. Of particular significance is information on any type of anticoagulant. At least three days prior to procedure, the patient should discontinue the anticoagulant medication including aspirin and aspirin derivatives. The patient should prepare himself for the procedure just like for blood donation i.e. on the previous day no fatty products are allowed to avoid lipemia. The patient should be in good general condition. On procedure day, he or she should have a light breakfast and be well hydrated.

In some patients however, blood collection is impeded by difficult vein access, intake of certain type of medications, or by an underlying disease. Autologous tears cannot be processed. Therefore, other ways of obtaining artificial tears from material of human origin are being sought.

Allogenic serum eye drops

Allogeneic preparations from blood donors are becoming more common [7, 8]. Their use is considered for both patients for whom autologous tears can be prepared as well as those for whom autologous tears are out of reach, e.g. children, people with difficult vein access, abnormal test results, or who are on drugs that might affect autologous preparations, *etc.*

Such patients can rely on artificial tears obtained from allogeneic serum of healthy male donors of the AB blood type. In such cases blood should be collected from donors tested for human leukocyte antigen (HLA) and/or human neutrophil antigen (HNA) antibodies or with no history of transfusions. To date, the risk related to the application of eye drops with antibodies has not been determined, but it is likely that antibodies may adversely affect therapy safety and outcome. Such donors must meet all eligibility criteria for infection markers as donors of blood dedicated for transfusion. They must test negative for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), syphilis and other infectious agents routinely tested in the country.

The advantages of autologous preparations are considerable: easier donor-patient access, quick collection procedure, no need for infectious marker testing, no risk of immunological reactions, and less anxiety related to application. Moreover, the procedure can be performed on an outpatient basis.

On the other hand, allogeneic preparations are produced in volumes that serve more patients. They can be mass produced and the quality standards more precisely defined and subject to strict legal regulations. Indeed, for safety reasons, legal regulations should be defined with regard to both allogeneic and autologous preparations.

Alternative sources of artificial tears

There is ongoing research into obtaining artificial tears with different techniques and from source material other than serum, namely platelet lysate and umbilical cord blood. Platelets are rich in growth factors that support wound healing. Approximately 70% of growth factors are secreted during clot formation. Current investigations are focused on finding an optimal preparation method to obtain artificial tears containing more growth factors than serum. A simple method, which has been known for years, is that of preparing platelet lysate through repeat freezing-thawing. There is no one standardized method of obtaining artificial eye drops from platelets. However, platelets seem an important source material for production of eye drops richer in some growth factors than autologous or allogeneic serum. This should directly translate to better therapeutic efficacy [9].

The scope of research into the possible use of umbilical cord blood (CB) is very broad. Well-recognized is the use of CB as a source of stem cells for managing malignant and non-malignant hematological disorders and immunological diseases. Research indicates that CB can also be used for the regeneration of other tissues. Numerous studies have demonstrated the efficacy of eye drops obtained from cord blood serum. Studies have been performed on preparates obtained from pooled CB [10]. The content of epidermal growth factor (EGF) was found to depend on the mother's age and type of delivery (vaginal vs. Cesarean section). Such a method of obtaining eye drops (EDs) allows for better choice of the starting material, performance of testing before eye drops are issued to the patient, and the selection of units with a higher content of healing factors [11].

Regardless of the preparation method, a universal challenge surrounds the storage of eye drops. EDs from both serum and platelet lysate require storage at temperatures below minus 18°C. An alternative could involve the preparation of lyophilisate plasma rich in growth factors, but this requires special techniques and equipment [12]. Preliminary research indicates that such preparates have good healing properties.

Our own experiences

IHTM has been preparing autologous artificial tears from serum for over 40 years. Currently, about 150 preparates are obtained annually. Each preparation gives c.600–1,500 single doses of artificial tears. Preparates are issued to patients immediately after the procedure together with instructions for freezing within 18 hours of collection and storage below –18°C. For artificial tears stored in such conditions, the expiry date is 12 months. No serious adverse reactions have been reported. Patients are instructed to discontinue applying artificial tears if dry eye symptoms exacerbate. Immediately after applying artificial tears, some patients experience sticking eyelids and blurred vision due to serum viscosity. Observations of patients with chronic GvHD and co-existing DES demonstrate their effectiveness as supportive therapy [13].

In cooperation with children's treatment centers (Children's Health Center, Clinic of Pediatrics, Hematology and Oncology the Medical University of Warsaw) the IHTM has participated several times in the preparation of autologous artificial tears for children with diseases other than DES. The outcome of such therapy was also found to be effective [14]. In the case of children, such preparates are difficult to obtain and other options must be considered, e.g. allogeneic tears or tears from the serum of an adult relative.

In 2019, following the approval of the IHTM Bioethics Committee, research was launched into the possible use of allogeneic preparations. Preliminary results are very promising [15]. During the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, allogeneic preparations have gained a special significance. Patients are discharged with pre-prepared frozen allogeneic preparations and therefore their stay on the IHTM premises is minimized, as is the risk of infection transmission. Patients who consent to this study are required to evaluate the effectiveness of the artificial tears by completing a questionnaire developed by IHTM. The questionnaire is based on a standard survey used in ophthalmology to assess the severity of the DES. In 2020, such preparates were issued to 14 patients.

Summary

DES is a growing problem which affects not only elderly people and patients subjected to stem cell transplants. It contributes to deterioration in the quality of life. Finding optimal treatment options for patients who cannot use medicinal products, or for whom such products are inefficient, is a huge challenge worldwide. The growing number of publications on the subject shows the necessity of satisfying the needs of such patients [3]. In order to evaluate the best therapeutic option, specialists in various fields should cooperate. Development of an optimal method of obtaining EDs cannot be achieved without collaboration

between transfusion medicine and other specialties including ophthalmology. Our study also indicates that therapy should be adjusted to the individual characteristics of each patient.

In many countries, ophthalmology societies issue guidelines for the use of preparations of human origin in patients with DES. Serious challenges to the development of uniform standards are the variety of preparation methods, the origin of the starting material, and the use of quality control or the applicable legal regulations.

Procedures for EDs preparation from material other than autologous serum are being gradually implemented in different centers, which proves that patient needs are diverse and many cannot benefit from autologous EDs. It has been pointed out that allogeneic artificial tears may have advantages over autologous tears. The latter may not be sufficiently effective and can sometimes even aggravate symptoms because they come from people with autoimmune diseases.

In view of the above, further research is called for. Efforts should be directed at the development of the most uniform preparation methods and quality standards for each type of preparation.

Author's contributions

JA-P — sole author.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

References

1. Wytyczne PTO, PTR, PTHiT dot. zapobiegania i leczenia ciężkiego zapalenia rogówki w przebiegu ZSO. https://pto.com.pl/aktualnosci//wytyczne-pto-ptr-pthit-dot-zapobiegania-i-leczenia-ciezkiego-zapalenia--rogowki-w-przebiegu-zso (June 5, 2020).
2. Valencia Castillo SL, Sáez Martín E, García Frade LJ, et al. Autologous serum eye drops improve tear production, both lachrymal flow and stability tests and conjunctival impression cytology with transfer in dry eye disease. Blood Transfus. 2021; 19(1): 45–53, doi: 10.2450/2020.0009-20, indexed in Pubmed: 32530402.
3. Higuchi A. Autologous serum and serum components. Invest Ophthalmol Vis Sci. 2018; 59(14): DES121–DES129, doi: 10.1167/iovs.17-23760, indexed in Pubmed: 30481816.
4. Marks DC, Fisher J, Mondy P, et al. Serum eye drop preparation in Australia: current manufacturing practice. Transfus Apher Sci. 2015; 53(1): 92–94, doi: 10.1016/j.transci.2015.05.015, indexed in Pubmed: 26123029.
5. von Hofsten J, Egardt M, Zetterberg M. The use of autologous serum for the treatment of ocular surface disease at a Swedish tertiary referral center. Int Med Case Rep J. 2016; 9: 47–54, doi: 10.2147/IMCRJ.S97297, indexed in Pubmed: 27042143.
6. European Committee (Partial Agreement) on Organ Transplantation (CD-P-TO). Guide to the quality and safety of tissues and cells for human application. 4th edition. European Directorate for the Quality of Medicines & HealthCare (EDQM), Strasbourg 2019: 413–415.
7. van der Meer PF, Seghatchian J, de Korte D. Autologous and allogeneic serum eye drops. The Dutch perspective. Transfus Apher Sci. 2015; 53(1): 99–100, doi: 10.1016/j.transci.2015.05.017, indexed in Pubmed: 26138910.
8. Marks DC, van der Meer PF. Biomedical Excellence for Safer Transfusion (BEST) Collaborative. Serum eye drops: a survey of international production methods. Vox Sang. 2017; 112(4): 310–317, doi: 10.1111/vox.12502, indexed in Pubmed: 28332214.
9. Zhang J, Crimmins D, Faed JM, et al. Characteristics of platelet lysate compared to autologous and allogeneic serum eye drops. Transl Vis Sci Technol. 2020; 9(4): 24, doi: 10.1167/tvst.9.4.24, indexed in Pubmed: 32818111.
10. Versura P, Profazio V, Buzzi M, et al. Efficacy of standardized and quality-controlled cord blood serum eye drop therapy in the healing of severe corneal epithelial damage in dry eye. Cornea. 2013; 32(4): 412–418, doi: 10.1097/ICO.0b013e3182580762, indexed in Pubmed: 22955120.
11. Versura P, Buzzi M, Giannaccare G, et al. Cord blood serum-based eye drops: the impact of donor haematological and obstetric factors on the variability of epidermal growth factor levels. Blood Transfus. 2014; 12(Suppl 1): s44–s50, doi: 10.2450/2013.0115-13, indexed in Pubmed: 24120597.
12. Anitua E, de la Fuente M, Alcalde I, et al. Development and optimization of freeze-dried eye drops derived from plasma rich in growth factors technology. Transl Vis Sci Technol. 2020; 9(7): 35, doi: 10.1167//tvst.9.7.35, indexed in Pubmed: 32832240.
13. Antoniewicz-Papis J, Lachert E, Janik K, et al. Autologous artificial tears used for treatment of dry eye syndrome in patients with chronic graft versus host disease. Pol Arch Intern Med. 2017; 127(10): 705–707, doi: 10.20452/pamw.4127, indexed in Pubmed: 29162791.
14. Laguna PJ, Antoniewicz-Papis J, Szajkowska A, et al. Application of autologous artificial tears in a case of an 8-year-old girl with vernal keratoconjunctivitis (Spring Catarrh). Blood. 2017; 130: 4931.
15. Antoniewicz-Papis J, Sacharczuk E, Rosiek A, et al. Pilot studies on the possibility of applying allogenic artificial tears. Vox Sang. 2020; 115(Suppl 1): 183. The 36th International ISBT Congress Virtual Meeting, 12–16 December 2020.