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Review

Blood derived eye drops for the treatment of cornea and ocular surface diseases

Giuseppe Giannaccare[a,*], Piera Versura[a], Marina Buzzi[b], Laura Primavera[a], Marco Pellegrini[a], Emilio C. Campos[a]

[a] Ophthalmology Unit, Department of Experimental, Diagnostic and Specialty Medicine (DIMES), Alma Mater Studiorum University of Bologna, S.Orsola-Malpighi Teaching Hospital, Via P. Palagi 9, 40138 Bologna, Italy
[b] Emilia Romagna Cord Blood Bank-Transfusion Service, S.Orsola-Malpighi Teaching Hospital, Via Massarenti 9, 40138 Bologna, Italy

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ABSTRACT

The use of blood derived eye drops for the treatment of ocular surface disorders has become increasingly popular in recent years. The mechanism of action is the stimulation of cellular proliferation and migration by supplying an active mixture of growth factors and cytokines at the ocular surface, thus mimicking the function of the lacking natural tears. Blood derived eye drops have been used in the last decades for the treatment of a variety of ocular surface diseases, including mainly dry eye disease, persistent corneal epithelial defect, corneal ulcer, ocular surface burn, recurrent corneal erosion and limbal stem-cell deficiency. Among overall blood derived eye drops, both autologous (from the patients themselves) and homologous (from donors) products exist, with different advantages and disadvantages. Autologous serum, obtained from the patient's own peripheral blood, is the first introduced and most commonly used product. Despite several randomized clinical trials showed its safety and efficacy, a recent Cochraine meta-analysis failed to show significant results due to low evidence. Homologous sources including allogeneic serum obtained from healthy donors, and umbilical cord blood serum collected at the time of delivery, are efficient alternatives, especially when autologous serum therapy is contraindicated or not appropriate. Platelet-derived eye drops are prepared and used in various but poor standardized preparations, namely platelet-rich plasma, plasma rich in growth factors, and platelet lysate. Future perspectives of blood-derived products include the introduction of tailored eye drops, screened for the proper content of growth factors and cytokines according to each patient and ocular surface disease.

Contents

* Corresponding author at: Via Pelagio Palagi 9, 40138, Bologna, Italy.
E-mail address: giuseppe.giannaccare@gmail.com (G. Giannaccare).

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1. Introduction

The idea of utilizing blood-derived products as eye drops for the treatment of ocular surface diseases has been proposed few decades ago. In 1975, Ralph and co-authors developed a mobile ocular perfusion pump used to deliver autologous serum or plasma to the ocular surface of patients with chemical burns [1]. Ten years later, the use of autologous serum eye drops (SED) in the treatment of patients with Sjögren's syndrome-related dry eye was first reported in literature [2]. Thereafter, other blood-derived products for the treatment of ocular surface diseases have been introduced in the Ophthalmic practice. They consist of eye drops prepared either from patients' own peripheral blood serum (autologous source), such as autologous serum, platelet-rich plasma, plasma rich in growth factors and platelet lysate, or from donors (homologous source), such as allogeneic peripheral blood serum and umbilical cord blood serum. Blood-derived eye drops offer an advantage over conventional ocular therapies, serving not only as a tear substitute to lubricate the ocular surface, but also containing several biochemical components, thus mimicking natural tears more closely [3,4]. The effects of blood-derived products on proliferation, vitality and migration of corneal epithelial cells have been well documented in the past by both in vitro and in vivo experimental studies [5–7]. In particular, these products have been used for the treatment of a variety of ocular surface diseases, including mainly dry eye disease, persistent corneal epithelial defect, corneal ulcer, chemical burn, recurrent corneal erosion and limbal stem-cell deficiency.

2. Literature review: methods

Relevant articles published to April 2017 were searched using PubMed, Scopus and Medline databases, as well as through the reference lists of identified publications. Search terms included the following key phrases: blood-derived eye drops; autologous serum; cord blood serum; platelet-derived eye drops; platelet-rich plasma; plasma rich in growth factors; platelet lysate.

From the literature search, we identified a total of 95 studies reporting the clinical outcomes of blood-derived topical therapy in overall ocular surface disorders. These studies spanned 47 centres in 22 countries (Fig. 1), and most of them have been published in the last two decades (Fig. 2). The purpose of this review is to summarize biological properties, methods of preparation and clinical efficacy of blood-derived products used in the ophthalmic practice. Current challenges and future perspectives of overall blood-derived treatments are also discussed.

3. Growth factors and nutrients in ocular surface physiology

The "Ocular Surface System" includes cornea, conjunctiva, tear film, lachrymal and meibomian glands, and eyelids, all components linked functionally by continuity of the epithelia, by innervation, and by the endocrine, vascular and immune systems [8].

The cornea is an avascular and transparent tissue, acting as a barrier for the intraocular structures, and accounting for approximately two-thirds of overall refractive power. It receives oxygen and nutrients by diffusion from the surrounding aqueous humour and tear film. Several corneal physiological functions, such as cellular turnover, wound healing and maintenance of transparency are modulated via paracrine/autocrine pathways by soluble factors present in the tear film. Various types of growth factors, such as epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor (TGF), keratinocyte growth factor (KGF), hepatocyte growth factor (HGF), nerve growth factor (NGF), platelet-derived growth factor (PDGF) and insulin-like growth factor (IGF) play a key role in ocular surface wound healing [9]. These growth factors and their receptors, expressed in the corneal epithelial cells, keratocytes and endothelial cells, promote the proliferation and the migration of corneal cells. EGF is secreted by lachrymal glands and corneal epithelium, and stimulates the proliferation and migration of corneal epithelial cells. Conversely, TGF-β inhibits epithelial cell proliferation while promotes epithelial migration and proliferation of corneal fibroblasts [9,10]. NGF is a neurotrophin that stimulates growth and survival of sensory and sympathetic neurons, restoring the function of injured neurons [11]. The human cornea produces NGF and expresses its receptors [12]. NGF plays a key role in the integrity and function of the ocular surface, stimulating both epithelial and nerve fibres proliferation and survival [13].

In addition to the above mentioned growth factors, fibronectin is an adhesive glycoprotein present both in tears and in the basement membrane of the ocular surface epithelium. It has a pivotal role in cellular migration, acting as a temporary matrix over which epithelial cells migrate during the wound healing process [14]. Vitamin A is also present in the tear film, and is necessary for the normal growth and differentiation of the corneal and conjunctival epithelium [15].

4. Autologous serum eye drops

Autologous SED are obtained from patients' own peripheral blood serum. Technical details and parameters of preparation including clotting time, centrifugation and dilution have been shown to influence the quality and the properties of the final product, and to date no internationally harmonized method for their production exists [16]. However, a standardized protocol was proposed, among Others, by Liu in order to optimize the concentration of the epithelia-trophic factors and the efficacy of the eye drops [17]. Briefly, 50–100 mL of whole blood is taken from the patient and is left for 2 h at room temperature without any anticoagulant for reaching a complete clotting. Next, the blood is centrifuged at $3000 \times g$ for 15 min to separate completely serum from solid components. The supernatant is then collected and diluted with balanced salt solution (BSS) to the desired concentration. Autologous serum can be stored at $-20\,^{\circ}C$ for several months, and the maximum interval of storage varies according to the local Legislation of each country. It should be kept away from light to avoid vitamin A degradation [17].

A recent international survey of SED production methods showed that approximately half of the centres dilutes serum prior to dispensing [18]. The rational for diluting the serum is to decrease to a physiologic concentration the levels of potentially anti-proliferative factors, such as TGF-β, which has shown to suppress corneal wound healing and promote corneal stromal fibrosis and opacity in vitro [9,10]. In fact, TGF-β is known to drive the development of mature myofibroblasts in the corneal stroma after injury; the disorganized extracellular matrix produced by myofibroblasts can cause corneal loss of transparency [19]. However, dilution also reduces at the same time the concentration of trophic