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Major review

Ophthalmic use of blood-derived products

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ABSTRACT

There is a wide spectrum of blood-derived products that have been used in many different medical and surgical specialties with success. Blood-derived products for clinical use can be extracted from autologous or allogeneic specimens of blood, but recombinant products are also commonly used. A number of blood derivatives have been used for a wide range of ocular conditions, from the ocular surface to the retina. With stringent preparation guidelines, the potential risk of transmission of blood-borne diseases is minimized. We review blood-derived products and how they are improving the management of ocular disease.

1. Introduction

Whole blood and various derivatives of blood have been used for a wide range of ophthalmic needs. These derivatives include fibrin-based products, albumin, umbilical cord blood serum, autologous and allogeneic serum, cryoprecipitate, platelets, plasmin, and fresh frozen plasma. Their use extends from the application of autologous serum (AS) to the ocular surface to the use of whole blood on the retina during vitreoretinal surgery. Early reports of the use of blood-derived products date back to 1946 when Katzin et al described the use of fibrin experimentally in the fixation of corneal transplants in rabbit models.[148] We review the use of blood-derived products in the management of ocular disease.

2. Serum

Serum is the noncellular supernatant left when whole blood clots (Fig. 1). Both autologous and allogeneic serum have been used in the management of ophthalmic disease. Most of the literature pertains to serum drops in the management of

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ocular surface disease, but it may also be used as an adjuvant in vitreoretinal surgery, particularly for macular holes.

2.1. Ocular surface disease

2.1.1. Science and theory

Contributors to ocular surface disease include lack of mechanical lubrication as well as a reduction in epitheliotrophic factors essential for ocular surface health.[106] Epitheliotrophic factors are present in varying concentrations in tears and include vitamin-A, substance P, insulin-like growth factor 1, nerve growth factor, epidermal growth factor (EGF), fibronectin, transforming growth factor (TGF)-β and other cytokines. Early reports showed that EGF promotes growth and migration of corneal epithelial cells and corneal epithelial healing.[248,343] Fibronectin found in tears has been used topically with success for persistent epithelial defects.[108,253] Substance P and insulin-like growth factor have a synergistic effect on corneal epithelial cell migration in a rabbit model,[229] and TGF-β stimulates proliferation and migration of stromal fibroblasts and regulates epithelial proliferative effects of other growth factors.[160] Serum has many of these same epitheliotrophic factors[108,205,209,230,253,255,266] found in tears and is applied to the eye under the premise that these factors may aid in healing of ocular surface disease.[323] Table 1 compares the relative concentrations of epitheliotrophic factors in tears with different blood preparations. Serum also contains immunoglobulins that provide bactericidal and bacteriostatic effects.[197] The pH, osmolality, and biomechanical characteristics of AS resemble those of natural tears,[191] making it suitable for ocular surface use as by its nature it is non-allergenic.[254]

Most studies highlight the use of AS in the treatment of ocular disease as it minimizes concerns of donor disease transmission.[39] Growth factor levels found in the serum of patients suffering dry eye are similar to levels found in control subjects, suggesting that AS drops are potentially as efficacious as allogeneic serum drops taken from healthy donors.[39] In circumstances where patients are unable to donate blood or AS because their use is contraindicated owing to systemic bacterial infections or acute autoimmune disease, allogeneic serum is an alternative.[56] There are a few reports on the use of allogeneic serum eye drops in dry eye patients and in patients with persistent epithelial defects, with similar efficacy to AS.[56,57,118,191,219]

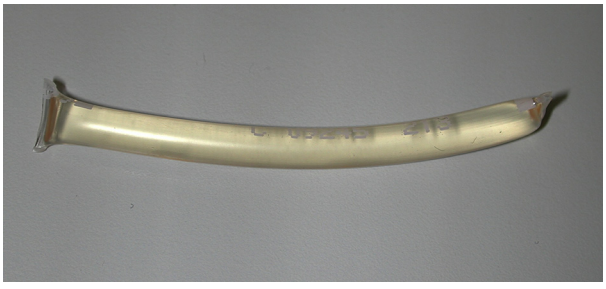

Fig. 1 – Plastic vial containing serum. The patient cuts one end with a clean pair of scissors for each use.

2.1.2. Dry eye

Fox et al were the first to report the use of AS in patients with dry eye.[95] Fifteen years later Tsubota et al described the use of AS for dry eye in Sjögren syndrome.[322] Since that time there have been a number of randomized controlled trials pertaining to the use of AS eye drops for dry eye. In these trials, patients had dry eye due to multiple etiologies including idiopathic keratoconjunctivitis sicca, Sjögren syndrome, and post–laser-assisted in situ keratomileusis (LASIK)/laser epithelial keratomileusis (LASEK) dry eye. Table 2 compares randomized, controlled trials highlighting the use of serum for the treatment of dry eye disease.

Tananuvat et al compared the effect of 20% AS in one eye against a placebo in the opposing eye in 12 patients with severe dry eye syndrome. Both AS and the placebo were able to improve subjective symptoms and objective signs with no statistically significant difference between the groups.[313] Noble et al undertook a prospective clinical crossover trial comparing 50% AS with conventional treatment. There was a significant improvement in subjective symptoms using AS, but no improvement in rose bengal staining, Schirmer test, or fluorescein clearance test. All patients had undergone punctual occlusion prior to the trial.[231] In another study by Kojima et al comparing preservative-free artificial tears (PFAT) against 20% AS for severe dry eye disease, there was a greater improvement in subjective symptoms as well as objective signs including mean tear break-up time and rose bengal and fluorescein staining in the serum group.[164] The patients in this trial were not masked as to the treatment received.[42] Urzua et al compared artificial tears with 20% AS over a 2-week period and found no difference in objective ocular surface indicators, although AS did improve ocular surface disease index (OSDI) scores. The lack of improvement in objective signs may have been a result of the short length of the trial.[330] Noda-Tsuruya et al compared the use of AS drops and artificial tears in a cohort of patients who had undergone LASIK and subsequently developed dry eye. After 6 months of treatment, tear break-up time and rose bengal corneal staining improved in the AS group. There was no change in the group receiving artificial tears. Interestingly, in this trial, subjective symptoms scores where similar between the groups after 6 months of treatment.[232]

Celebi et al[49] conducted a double-blind crossover study comparing 20% AS with PFAT in severe dry eye syndrome refractory to conventional treatment. Ocular surface symptoms improved in both groups after a month of treatment, but improved more significantly in the AS group (the mean OSDI score in the AS group was 26.5, vs 43.2 in the PFAT group). After a 2-week washout, OSDI scores tended toward pretreatment baselines (54.8 in the AS group and 55.7 in the PFAT group). After crossover and a further month of treatment, OSDI scores were better in the group now receiving AS compared with scores of those using PFAT (OSDI score 24.8 vs 43.2).

Other non–trial-based reports purport benefits of AS drops.[69,143,187,255,311,318] Most reports (including the randomized controlled trials) differed in the number of drops given daily, perhaps explaining variations in efficacy.[311] Combination therapy for dry eye, including the use of serum eye drops