Review Article

Biological topicals in ocular surface disorders

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Topical biological agents represent a significant advancement in the treatment of ocular surface diseases, offering a regenerative and therapeutic approach beyond conventional therapies. These agents are derived from serum (autologous or allogeneic), platelets, amniotic membrane, and pooled intravenous immunoglobulin. Their efficacy stems from their rich composition of growth factors, cytokines, and anti-inflammatory molecules that promote tissue healing, reduce inflammation, and enhance corneal regeneration. Autologous serum eye drops, closely mimicking natural tears, have been widely utilized for conditions such as dry eye disease, neurotrophic keratopathy, and persistent epithelial defects. Similarly, platelet derivatives, including platelet-rich plasma (PRP) and platelet lysate (PL), have demonstrated accelerated wound healing and nerve regeneration benefits. Amniotic membrane extracts and human amniotic fluid eye drops share the anti-inflammatory and regenerative properties of the human amniotic membrane. Recent advancements have introduced the use of topical IVIG, which modulates immune responses in severe inflammatory dry eye conditions, such as ocular graft-versus-host disease. Despite these promising applications, challenges such as variability in preparation, storage limitations, and cost remain. Nevertheless, the future of topical biological agents is promising, with emerging recombinant therapies and personalized treatment approaches shaping modern ophthalmologic care. As research continues to expand, these agents are poised to become integral components in managing ocular surface disorders, improving patient outcomes, and reducing dependence on traditional therapies.

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Topical biological agents offer a promising therapy for various ocular surface diseases, especially when conventional treatments are insufficient. Derived from natural sources, these agents—such as autologous and allogeneic serum, platelet derivatives, amniotic membrane extracts, and intravenous immunoglobulin (IVIG)—leverage biological molecules to promote tissue repair and regeneration.[1,2] Autologous serum drops, rich in growth factors, vitamins, and proteins, have shown significant efficacy in treating ocular surface disorders such as dry eye and neurotrophic keratopathy.[3] Similarly, topical platelet derivatives, including platelet-rich plasma (PRP), plasma-rich growth factors (PRGFs), and platelet lysate (PL), have demonstrated their role in accelerating wound healing and tissue regeneration.[4,5] Amniotic membrane extract, with its anti-inflammatory and regenerative properties, has proven effective in managing chronic corneal ulcers and post-surgical corneal epithelial healing.[6] More recently, IVIG, owing to its immune-modulating properties, has been employed topically for treating dry eye disease of various aetiologies.[7] This review explores the mechanisms, indications, and clinical outcomes of topical biological treatments, highlighting their growing role in modern ophthalmic care.

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Methods of Literature Search

A systematic literature search was conducted using PubMed, Google Scholar, and Cochrane Library databases. The following keywords were used as follows: topical, autologous, serum, amniotic, membrane, extract, platelet, immunoglobulin, and lysate. Relevant review articles, original articles, case series, and case reports were reviewed. The search was conducted in October 2024. We limited our search to articles published from 1975 to 2024 and were written in English.

Serum-Derived Topical Biological Agents

Human tear film is rich in biologically active 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). These factors play key roles in cellular proliferation, migration, differentiation, and survival.[8] The proposed benefits of blood-derived topical agents arise from their composition, which closely resembles that of human tears, in contrast to artificial tears that primarily provide lubrication. The use of blood-derived products such as

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eye drops was pioneered by Ralph *et al*.[9] in 1975, who utilized a continuous ocular perfusion pump to deliver undiluted autologous and homologous serum in patients with chemical burns, chronic viral keratitis, and ocular pemphigoid. Fox *et al*.[10] later reported using diluted autologous serum to treat refractory keratoconjunctivitis sicca. Over the years, several types of blood-derived products have been explored for topical therapy. These can be of autologous origin, such as serum, PRP, PRGFs, and PL, or of allogeneic origin, such as peripheral blood serum, umbilical cord serum, and topical immunoglobulin.

Autologous serum eyedrops

Autologous serum (AS) eye drops, derived from a patient's own blood, are the most commonly used blood-based topical biological agent. The composition of AS closely resembles that of human tears but contains higher levels of vitamin A, lysozyme, TGF-β, and fibronectin, while IgA, EGF, and vitamin C are lower.[11,12]

Mechanism of action

Topical AS primarily functions through three main mechanisms: lubrication, improved epithelial healing, and reduced inflammation. It is rich in growth factors, vitamins, and fibronectin, essential for the growth and repair of the ocular surface epithelium. Beyond promoting epithelization, the serum contains neurotrophic factors (NGF, IGF, and substance P) that enhance corneal sensitivity[13,14] and nerve structure recovery.[3,15] Anti-inflammatory factors, such as interleukin (IL)-1 receptor antagonists and tissue inhibitors of metalloproteinases, help reduce ocular surface inflammation that indirectly enhances epithelial viability.[16,17] Furthermore, albumin in the serum prevents cell death in conjunctival cells, while its antimicrobial components—lysozyme, lactoferrin, and immunoglobulins—reduce the risk of infection.[18]

Preparation

There is no standardized protocol for the preparation, processing, or storage of AS eye drops, and various methods have been described in the literature.[11,14,16,18–22] Most authors follow a protocol based on the one outlined by Liu *et al*.[11] In this method, 100 mL of the patient's blood is collected into sterile containers, followed by routine virology screening. The blood is then left to stand at room temperature for 2 hours before being centrifuged at 3,000 × g. The serum supernatant is transferred to disposable syringes under sterile conditions in a laminar airflow hood, following which it is diluted 1:4 with balanced salt solution (BSS) and aliquoted into sterile dropper bottles. The prepared eye drops are stored at −20°C for up to 3 months. Once opened, the bottle is stored at +4°C and discarded after 16 hours of use as per the original protocol.[11] While it is generally recommended to store AS at −20°C for 3 months, studies show that epitheliotropic properties remain stable for up to 6 months at this temperature.[23] A closed manufacturing system, designed to ensure sterility and reduce contamination risk, has also been described.[17] In addition to BSS, agents such as normal saline, hyaluronic acid, and antibiotics, have been used to dilute AS. Serum diluted with BSS was found to promote epithelial cell growth more effectively than isotonic saline.[11] Better outcomes were reported with AS diluted in hyaluronate, in terms of improved tear stability and symptoms, requiring fewer drops, and better tolerance.[24] However, another report found no benefit of dilution with 0.3% hyaluronate and observed poorer outcomes when AS was diluted with antibiotics, possibly due to toxicity.[21]

Table 1 provides an overview of the various protocols described in the literature for preparing AS eye drops.

Dosage and frequency

Concentrations of AS drops used clinically range from 20% to 100%. Since the serum is rich in TGF-β, a pro-inflammatory cytokine, a 20% concentration is often recommended to reduce its levels similar to those in natural tears.[18,25] Higher concentrations (33–100%) have been used in severe cases.[26,27] The recommended frequency of instillation ranges from every 2–3 hours to every 6 hours. However, most studies suggest frequent instillation due to the short duration of the physiological effect of the serum drops on the ocular surface.

Outcomes

AS eye drops have been found to be an effective adjunct in treating a range of ocular conditions, particularly those involving poor epithelial healing and corneal nerve dysfunction. They have been widely used for severe dry eye, Sjögren's syndrome, ocular graft-versus-host disease (GVHD), post-surgical dry eye, recurrent corneal erosions, persistent epithelial defects (PEDs), limbal stem cell deficiency (LSCD), and corneal neuropathic pain.[3,25,28–30]

The major benefits of AS treatment include faster corneal epithelial healing, better tear film stability, and symptomatic relief. Studies have shown significant improvements in both objective measures (tear film stability, corneal staining) and subjective symptoms, particularly in refractory or severe dry eye cases.[31–35] In Sjögren's syndrome, AS provides symptomatic relief and enhances ocular surface health[15,16,19,36,37] with higher concentrations showing greater benefit in more severe cases and a longer treatment duration being required for sustained results.[21,36] For post-surgical dry eye, AS accelerates healing and restores visual acuity, particularly in laser-assisted *in situ* keratomileusis (LASIK) and penetrating keratoplasty patients.[38–42] Furthermore, AS is effective in reducing symptomatic episodes in cases of recurrent corneal erosions.[43,44] AS demonstrated higher success rates and faster healing times compared to conventional treatments for PEDs.[25–27,45–48] Combining AS with bandage contact lenses also proved to be beneficial. AS was also found to be a useful adjunct in ocular reconstruction surgery and treating aniridic keratopathy, contact lens-associated LSCD, glaucoma surgery, and drug-induced LSCD.[26,47,49–56] AS drops were effective in treating photoallodynia in patients suffering from corneal neuropathic pain.[57,58] Table 2 summarizes the clinical outcomes of AS eye drops in ocular surface disorders.

Adverse Effects: Adverse events related to AS eye drops are rare, with the more commonly reported side effects being ocular discomfort, redness, watering, itching, reduced sensitivity, lid swelling, conjunctivitis, and sticky sensation.[27,59,60] Less frequently, immune complex deposition, sterile infiltrates on the cornea, and albumin deposits on contact lenses have been observed.[21,27,50,61] Microbial keratitis, though an extremely rare occurrence, has been reported typically in the presence of risk factors such as PED, contact lens use, or improper storage of the serum.[27,62]

Barriers and challenges in using autologous serum eyedrops

Despite its effectiveness, AS eye drops present certain challenges, including potential variability in composition due

Table 1: Protocols for preparation of autologous serum eyedrops in ocular surface disorders

	Clotting time	Centrifugal force	Duration of centrifugation	Dilution	Diluent	Storage conditions	Other components
Liu L *et al*.[11]	Blood left upright for 2 h at room temperature	3000 g	15 min	1:4	Sterile-balanced salt solution	Stored at –20°C for up to 3 months	No preservatives; opened vials stored at +4°C for 16 hours
SOP for National Blood Service in England and Wales[18]	Blood stored at +4°C for 2 days	2000 rpm	5 min	1:1	Sterile normal saline	Stored at –20°C until patient collection	Bacterial culture on five samples from each batch; no preservatives or antibiotics added
SOP at the University of Lu ̈beck, Germany[18]	Blood left standing for 2 h at room temperature	3000 g	15 min	1:5	Sterile-balanced salt solution	Stored at –20°C	Filter sterilized; aliquoted into sterile dropper bottles
Tsubota K *et al*.[16]	-	1500 rpm	5 min	20%	Sterile normal saline	Stored in the freezer; opened bottle in the fridge	Ultraviolet light protection; to preserve Vitamin A
Ogawa Y *et al*.[14]	-	1500 rpm	10 min	20 %	Sterile normal saline	Stored at –20°C until use. Once thawed at 4°C for 10 days	Added 0.3% ofloxacin
Hussain M *et al*.[19]	Blood is allowed to clot for 15 min at room temperature	14,000 rpm	15 mins	50%	Sterile normal saline	Unopened vials stored at –20°C; opened vials at +4°C	Filtered through 0.22 mm filter; used aseptic technique
Lagnado R *et al*.[20]	Blood clotted at 4°C for 10–12 h	4500 rpm	15 min	20%	Sterile normal saline	Unopened vials stored at –20°C; opened vials at +4°C	2.0 mL aliquots, thawed for daily use
Cho YK *et al*.[21]	Blood clotted at room temperature for 5 min	3000 rpm	5 min	100%, 50%	Normal saline/ artificial tears (0.3% sodium hyaluronate)/ antibiotic (0.5% ceftazidime)	Unopened vials stored at–20°C; opened vials at +4°C	Aliquoted in sterile bottles in a laminar flow cabinet
Vazirani J *et al*.[22]	Blood clotted at room temperature for 30–60 min	2500–3000 rpm	–	20%	Sterile normal saline	Stored at–20°C. Opened vials at 4°C	Dispensed 5 mL each in sterile dropper vials

SOP – standard operating procedure; rpm – revolutions per minute

to the patient's systemic status and preparation process.[18] Autoimmune conditions like Sjögren's syndrome and GVHD can elevate inflammatory cytokines in tears and serum, potentially reducing treatment efficacy, especially in secondary Sjögren's syndrome.[37] However, most studies suggest autoimmune disorders do not significantly impact the clinical outcomes and epitheliotropic properties of AS.[63–66] Composition of AS is also affected by preparation factors like centrifugation time and g-force, with longer clotting times and higher g-force enhancing levels of beneficial growth factors.[2,16] Other limitations include microbial contamination risks, the need for cold storage, frequent blood draws, and high processing costs.[19]

Allogeneic serum eye drops

While the AS is effective for treating severe dry eye symptoms, its use may be limited by challenges such as poor venous access, low hemoglobin levels, hematological disorders, use of anticoagulants, and age-related issues, which can make blood collection difficult.[67] Additionally, serum from patients with Sjögren's syndrome or GVHD may contain elevated levels of pro-inflammatory mediators which could have deleterious effects on the ocular surface. Systemic factors, such as immunosuppression in rheumatoid arthritis or chronic kidney failure patients, may also reduce the epitheliotropic properties of the serum, requiring higher concentrations for optimal results.[64,68] Furthermore, preparing AS eye drops often involves significant waiting times, which can delay treatment. Allogeneic serum overcomes the challenges of AS by allowing collection and processing in advance, thus ensuring immediate availability.[69]

Donor selection and preparation

While the method of preparing allogeneic serum eyedrops is similar to that described for AS, drops careful donor selection and screening are crucial, and informed consent from the donor is mandatory.[60,69] Despite theoretical risks like immune reactions from ABO mismatches or HLA antibodies, on using allogeneic serum eyedrops, clinical use shows that ABO compatibility is not needed, with no hypersensitivity being observed.[70,71] To further reduce these risks, male donors without transfusion history and AB blood group are preferred. ABO-specific allogeneic serum from volunteer male donors may also be used.[59,72] A four-month quarantine and re-testing of the donor serum before use minimize risks of infection transmission. Unlike AS, allogeneic serum can be used for multiple patients.[69]

Table 2: Clinical outcomes of autologous serum eye drops in ocular surface disorders

Indication	Concentrations used, instillation frequency, and treatment duration	Outcomes
Severe/refractory dry eye[31-35]	Concentration – 20–50% Frequency – 4 to 10 times/day Duration of treatment – 2 weeks to 3 months	Superior to conventional treatments in improving tear stability, corneal staining, cytology, and symptom relief. Significant improvement in both objective and subjective measures.
Sjögren's syndrome associated dry eye[16,19,21,36,37,45]	Concentration – 20–50% Frequency – 3 to 8 times/day Duration of treatment – 4 weeks to 12 months	Symptomatic relief, improved ocular surface staining, and TBUT. Longer treatment duration (up to 3 months) is recommended for better outcomes. Undiluted AS is more effective. A total of 50% AS showed improvements after 4 weeks of therapy. Combination with punctal plugs shows additive effects. Early treatment and severity of baseline dry eye are key determinants. Secondary Sjögren's syndrome showed a poorer response. Lower concentration (20%) and extended treatment duration may offer better results in these cases
Ocular GVHD[14,17,29,30,59]	Concentration – 20–100% Frequency – 4 to 10 times/day Duration of treatment – 6 to 70 months	Significant improvement in TBUT, ocular staining, and symptom relief, especially in transplant patients with severe dry eye 100% AS in single-use vials found to be safe and effective.
Post-surgical indications[38-42]	Concentration – 20–50% Frequency – 5 times/day to one hourly Duration of treatment – 7 days to 6 months	Improved tear film stability and reduction in epithelial damage in LASIK patients. Enhances ocular surface and visual acuity in recalcitrant LINE cases. Accelerates epithelial healing in post-penetrating keratoplasty (20% AS), pterygium excision (50% AS), and post-vitrectomy patients (50% AS).
Recurrent corneal erosions[43,44]	Concentration – 20–50% Frequency – 3 to 6 times/day Duration of treatment – 3 to 6 months	85% healing with a reduction in recurrent episodes of corneal erosion and sustained benefits over long-term follow-up.
Persistent epithelial defects[25-27,45-51]	Concentration – 20–100% Frequency – 1 hourly to 14 times/day Duration of treatment – 1 to 4 weeks	Described for treating PEDs in indications, including neurotrophic keratoplasty, chemical injuries, SJS, vernal keratoconjunctivitis, and post-surgical PED. Superior to conventional treatment in terms of higher success rate (46–74% heal within 4 weeks) and shorter re-epithelialization time and recovery of corneal sensitivity Undiluted AS had a success rate of 87% with a median healing time of 14 days Combined use with bandage contact lenses improves outcomes.
Limbal stem cell deficiency[52-55]	Concentration – 20–50% Frequency – 2 hourly to 8 times/day. Duration of treatment – 2 to 53 months	Found to be useful as an adjunct in ocular reconstruction procedures and treating AAK of mild-moderate severity, reversal of severe contact lens-associated LSCD, stabilization of glaucoma surgery-induced LSCD, and capecitabine-associated LSCD. More effective than conventional tear substitutes in improving ocular surface, corneal epithelialization, and squamous metaplasia in AAK. Intensive treatment (20% AS) alleviated symptoms and reversed clinical signs of severe contact lens-induced LSCD 50% AS had a limited role in stabilizing the progression of LSCD in post-glaucoma surgery-induced LSCD
Corneal neuropathic pain[57,58]	Concentration – 20% Frequency – 8 times/day	Reduction in photoallodynia after a mean period of 3.6 months of treatment. A total of 56.25% of patients demonstrated more than 90% improvement in symptoms. Improvements were observed in corneal nerve density, morphology

AS – autologous serum; GVHD – graft-versus-host disease; TBUT – tear break-up time, LASIK – laser-assisted *in situ* keratomileusis; LINE – LASIK-induced neurotrophic epitheliopathy; AAK – aniridia-associated keratopathy; LSCD – limbal stem cell deficiency; PED – persistent epithelial defect; SJS – Stevens-Johnson syndrome

Outcomes

Studies have demonstrated that the efficacy and safety of allogeneic serum eye drops are comparable to AS for conditions such as severe dry eye, PED, and ocular GVHD, making it a more convenient and accessible alternative when AS is unavailable or unsuitable.[67,69,72–74] This has led to increasing use of allogeneic serum eye drops, particularly those sourced from voluntary AB blood type donors.[75,76] Since 2003, 47% of patients in New Zealand receiving serum eye drop treatments have used allogeneic serum, with 30% receiving only allogeneic drops and 17% receiving a combination of both autologous and allogeneic serum.[76]

Umbilical cord blood serum

Umbilical cord blood serum (CBS), collected during vaginal or cesarean deliveries, offers an alternative to peripheral blood serum eye drops. Studies have reported higher concentrations

of growth factors like EGF, TGF-β, NGF, and VEGF in CBS compared to peripheral blood serum.[77–80]

Donor selection and preparation

CBS requires informed consent and screening of the donor for viral diseases (HIV and Hepatitis B and C), at the time of delivery. Additional testing for HIV at the time of delivery is required if more than 6 months have passed between testing and serum preparation.[81] Higher concentrations of EGF were associated with younger mothers (<30 years), longer labor (>6 hours), and higher CD34+ cell counts, as well as female sex and higher baby birth weight.[82,83]

Cord blood is collected from the umbilical vein under sterile conditions, without using an anticoagulant. The blood is allowed to clot (for 30 minutes to 2 hours) at room temperature before centrifugation, which is then typically performed at 1500–3000 rpm for 5–15 minutes. The serum is then separated and diluted to a 20% concentration, using sterile saline or BSS. The diluted serum is stored at −20°C, with microbiological culture tests conducted for each batch. After thawing, the serum is stored at 4°C, and patients are instructed to use an opened bottle within 7 days or a maximum of 3 months for unopened bottles.[78,84–86] The frequency of instillation ranges from 4 to 10 times a day.

Outcomes

The use of CBS has been reported to be effective in treating a variety of ocular conditions, including recalcitrant dry eye disease,[78,87–89] neurotrophic keratitis,[90] recurrent corneal erosions,[91] PED,[80,84,92] ocular GVHD,[79] Stevens-Johnson syndrome (SJS),[93] acute chemical burns,[85] and post-surgical epithelial healing following corneal laser ablation, penetrating keratoplasty, and vitrectomy.[94–96] Studies found CBS to be more effective than peripheral blood serum for moderate-to-severe dry eye, in terms of reducing corneal epithelial damage, improving symptoms, and restoring corneal nerve fiber properties.[81,86,88,97] Sharma *et al*. found that CBS accelerated epithelial healing and improved corneal clarity in chemical burn patients.[85] However, a recent study found comparable outcomes between CBS and AS for dry eye disease with a lower concentration of growth factors in CBS.[98]

Platelet-Derived Topical Biological Agents

Platelets are a rich source of biologically active molecules, including PDGF, EGF, FGF, TGF, NGF, IGF, and cytokines and chemokines that are stored in the alpha granules.[4] Platelet activation or rupture releases these growth factors. The major autologous blood-derived platelet preparations used to treat ocular surface disorders are PRP, PRGF, and PL, differing in platelet concentration and preparation methods.[5]

PRP is the primary platelet preparation, with a higher platelet concentration than whole blood, serving as a foundation for other platelet-derived products. PRP is rich in growth factors and has been used for aiding tissue regeneration across various medical fields.[99] PRGFs are a variant of PRP that lacks leucocytes, and activation with calcium chloride induces the release of biologically active proteins.[100] PL is similar to PRP but activated by a freeze-thaw process to facilitate the lysis of platelets, releasing a higher concentration of growth factors.[101]

Mechanism of action

PRP's high-platelet concentration leads to the release of growth factors and cytokines upon platelet aggregation and stimulation. These factors promote epithelial and mesenchymal cell migration and proliferation, aiding in the repair of damaged ocular surfaces.[99] Additionally, PRP provides lubrication, anti-inflammatory effects, and antibacterial peptides. Activation occurs at the site of application, ensuring a slow release of growth factors which prolongs the therapeutic effect. However, PRP's high leucocyte content may also release pro-inflammatory cytokines, potentially exacerbating local inflammation.[102,103]

Preparation

Platelet-rich plasma: PRP eye drops preparation in ophthalmology typically follows single-step or two-step centrifugation methods. In the single-step centrifugation method, blood is collected with sodium citrate, centrifuged at 1400 rpm, and PRP is separated. The final product is stored in amber glass bottles at −20°C for up to 3 months. The resulting PRP typically contains 1.6–2.5 times the platelet concentration found in whole blood.[102] In a modification of this method, blood is centrifuged at 1600 rpm, resulting in the separation of three layers: platelet-poor plasma at the top, PRP in the middle, and red/white blood cells at the bottom. The PRP layer is then aspirated and transferred into sterilized amber glass bottles.[103]

Plasma-rich growth factors: PRGFs are produced using a closed technique, as described by Anitua *et al*. Blood is collected with trisodium citrate and centrifuged at 580 g at room temperature using an Endoret System centrifuge (BTI Biotechnology Institute, Spain). The PRGFs are extracted, avoiding the buffy coat, activated, and incubated at 37°C. It is then heat-treated to remove immunologic components and stored at −20°C for up to 3 months.[104–107]

Platelet Lysate: PL is essentially PRP activated through a freeze-thaw process. The platelet concentrate is frozen at −80°C, then thawed to 37°C. The resulting lysate is diluted to a 30% concentration using sterile BSS and aliquoted into ready-to-use, sterile doses.[3,108] Multiple freeze-thaw cycles have also been described. Commercially available human platelet lysate preparations include UltraGRO™ (Helios, Atlanta, GA) and PLTMax (Mill Creek, Rochester, MI).[109] Table 3 details the properties and preparation of different platelet-derived eye drops.

Outcomes

Platelet-derived topical agents have emerged as promising treatments for various ocular surface disorders, such as moderate-to-severe dry eye, Sjögren's syndrome, ocular GVHD, post-LASIK dry eye, PEDs, dormant ulcers, neurotrophic keratopathy, recurrent corneal erosions, chemical burns, and ligneous conjunctivitis.[4,110]

Studies report improvements in subjective symptoms, dry eye-related signs, and visual acuity with platelet-derived eye drops and injections in patients with moderate-to-severe dry eye and Sjögren's syndrome. PRP has been found superior to lubricant drops in comparative studies.[111–117] PRP eye drops were comparable to AS in treating dry eye in both Sjögren's syndrome (SS) and non-SS patients, whether used undiluted or diluted, presenting an effective alternative to AS.[118–121] Conditions such as ocular GVHD may require longer treatment durations up to 6–12 months.[101,108,122] PL eye drops have been shown to improve corneal nerve morphology and basal epithelial cell density in SS patients.[115] While PRP eye drops

Table 3: Platelet-derived eye drops – properties, preparation and mechanism of action

Name	Properties	Preparation	Mechanism of action
Platelet-rich plasma (PRP)[102]	Contains high-platelet concentration; rich in growth factors and cytokines	- Blood collected in a 10 mL tube with 1 mL of 3.2% sodium citrate anticoagulant - Centrifuged at 1400 rpm for 10 mins at 5°C, - PRP is collected from the top 90% of plasma. - Aliquots of 3–4 mL of the PRP transferred into sterilized amber glass bottles - Stored at–20°C for up to 3 months; after opening vial stored at 4°C for up to a week	Platelets release growth factors and cytokines, promoting cell migration, repair, and regeneration. Provides lubrication, anti-inflammatory, and antibacterial effects
Platelet-rich growth factors (PRGF)[104-107]	Contains high-platelet concentration, lacks leucocytes, enriched in growth factors.	- Blood collected in 9 mL tubes with 0.9 mL trisodium citrate. - Centrifuged at 580 g for 8 minutes at room temperature. - PRGF is collected, avoiding the buff coat, activated with calcium chloride (50 µL per mL of PRGF), incubated at 37°C for 1 hour - Heat treated at 56°C for 60 minutes to remove immunologic components. - Filtered, aliquoted, and stored at–20°C for up to 3 months. Open dispenser used within 3 days	Upon activation, platelets release growth factors that promote cell migration, epithelial repair, lubrication, anti-inflammatory, and antibacterial effects, with a slow release of mediators
Platelet lysate (PL)[101]	Similar to PRP but with a higher concentration of growth factors due to platelet lysis	- PRP activated through a freeze-thaw process. - Frozen at–80°C and thawed to 37°C - Diluted to 30% concentration with sterile saline. - Stored at–20°C. Can be stored in the patient's freezer for up to 45 days.	Activated to release growth factors through freeze-thaw process, which enhances tissue regeneration, provides anti-inflammatory effects, and promotes cell migration

have been most extensively studied, many studies stored PRP drops at −20°C and instructed patients to keep them at 4°C. This inevitably leads to thawing and platelet lysis, making the drops behave more like PL than true PRP.[4]

Platelet-derived topical agents have also been explored for treating PEDs caused by neurotrophic factors, herpetic infections, immunologic conditions, post-corneal surgery, and chemical burns.[123–129] Complete epithelialization was observed in 50% to 85% of cases of neurotrophic keratopathy. Symptomatic improvement occurred in over 90% of cases, with visual acuity improving in more than 60%[123,125] and about 60% of post-surgical PEDs.[128,129] Notably, PRP was found to promote faster epithelial healing in post-microbial keratitis PEDs compared to AS.[126] Table 4 summarizes the clinical outcomes of various ocular surface disorders treated with platelet-derived eye drops.

Adverse Effects – Few adverse effects, none visually significant, have been reported with topical platelet derivatives, including burning sensation and ocular discomfort and eye irritation.[4,118,123]

Human Amniotic Membrane Derived Topical Agents

The human amniotic membrane is used to treat various ocular surface conditions, including dry eye disease, PEDs, neurotrophic keratitis, SJS, chemical burns, LSCD, and ocular surface reconstruction, owing to its anti-inflammatory, regenerative, and antimicrobial properties.[130] However, amniotic membrane transplantation carries potential drawbacks, such as a decrease in vision, post-surgical discomfort, and risks such as infection and tissue degradation. To address these limitations, derivatives such as amniotic membrane extract drops (AMED) and human amniotic fluid (HAF) drops have been investigated.[131] Moreover, AMED and AF when applied as eye drops allow prolonged treatment if required. More recently, human amniotic epithelial stem cell eye drops have been explored for the treatment of ocular GVHD.[132]

Mechanism of action

Human amniotic derivatives, such as AMED and AF, share the antimicrobial, immunomodulatory, and tissue-regenerative properties of the amniotic membrane. AMED is rich in growth factors like EGF, HGF, FGF, protease inhibitors, and the matrix component HC-HA/PTX3. These biomolecules promote corneal epithelial migration, adhesion, and differentiation while preventing apoptosis. They also downregulate inflammatory markers, reduce pro-inflammatory cytokine release, and prevent angiogenesis and scarring.[131,133] Processed HAF possesses these beneficial properties and has been used for treating ocular surface disorder.[134]

Preparation

Amniotic membrane extract eye drops: AMED is essentially a homogenized suspension derived from an amniotic membrane. Different methods have been described for preparing AMED, using either cryopreserved or fresh amniotic membranes. Amniotic membrane is obtained from the placentas of seronegative donors undergoing elective cesarean delivery after obtaining informed consent. Baradaran *et al*.[135] used cryopreserved amniotic membrane, processing it with antibiotics, freezing, grinding, and centrifuging to obtain AMEED, applied at a concentration of 0.5 mg/mL. Bonci *et al*.[136] used a simpler method that homogenized cryopreserved amniotic membrane with BSS and antibiotics. Sabater-Cruz *et al*.[137] prepared lyophilized AME from fresh amniotic membrane that could be reconstituted before use, offering the advantage of storage at room temperature. Commercially available lyophilized amniotic membrane extracts include AMX and FloGraft. Cheng *et al.* described the preparation of a morselized amniotic membrane and umbilical cord blood eye drops.[138] The method used to process the amniotic membrane can influence the composition of the extract. Pulverizing the membrane increased the level of growth factors (HGF) by 20% compared to homogenizing it. Additionally, centrifuging the extract up to three times nearly doubled the amount of growth

Table 4: Clinical outcomes of platelet-derived eye drops

Indication	Platelet derivatives used	Duration and frequency of instillation	Clinical outcomes
Dry eye disease[99,102,111-113]	PRP drops	Duration – 4–8 weeks Frequency - 4–6 times/day	PRP more significant and earlier improvement compared to artificial tears A total of 87–89% of patients experienced symptom improvement. About 28.8% had an improvement in CDVA. About 76.1% of eyes showed a significant decrease in clinical signs
Sjogren syndrome associated dry eye[114-117]	PRGF, PL, PRP injection	Duration – 3–12 months Frequency – 4 times/day	Significant improvement in symptoms (aPL and PRGF) and CDVA (PRGF) Basal epithelial cell density and sub-basal nerve plexus density significantly increased Inflammatory cells significantly decreased with aPL improvement in symptoms, corneal staining, TBUT, and tear volume with PRP injection
Ocular GVHD[101,108,122]	PL	Duration – 4–36 months Frequency- 4–6 times/day	73.9–91% of patients showed improvement in symptoms Remission of clinical signs in 86% of eyes. After 6 months of treatment, all patients showed improvement in symptoms, disease severity, TBUT, and corneal staining, maintained at 36 months
Post-LVC dry eye[99,112]	PRP eye drops	Duration – 6–12 weeks Frequency – 3–6 times/day	85% of patients showed improvement of symptoms Decrease in staining in 90% of patients. Conjunctival hyperemia improved in 93.3% of patients.
PED/dormant ulcer/neurotrophic keratopathy[103,126-129]	PRP eye drops PRGF eye drops	Duration – 4–11 weeks Frequency – 3–8 times/day	Significant decrease in time to re-epithelialization with PRP and PRGF About 59–100% PEDs healed About 90–100% improvement of symptoms Complete epithelialization was observed in 50% to 85% of cases of neurotrophic keratopathy. About 31–100% showed improvement in CDVA PRP hastened epithelial healing in post-microbial keratitis compared to autologous serum
Chemical injury[124]	PRP eye drops	Duration – 3 months Frequency – 10 times/day	The time to complete epithelialization is shorter in more severe chemical burns (grade 3) At 3 months, better corneal clarity in the PRP group as compared to conventional treatment

GVHD – graft-versus-host disease; TBUT – tear break-up time, CDVA – corrected distance visual acuity; PRP – platelet-rich plasma; PL – platelet lysate; PRGF – plasma rich in growth factors; PED – persistent epithelial defect

factors and proteins in the final product.[139] Table 5 details the various methods described for producing AMED.

Human Amniotic Fluid Eye Drops: HAF is obtained from seronegative volunteer donors undergoing cesarean deliveries, following the thorough screening. The collected fluid is stored at 2–8°C until processing. It is then centrifuged at 1400 g for 20 minutes at 4°C, and the resulting supernatant is filtered through a 0.2 mm filter to sterilize and remove cellular debris, ensuring a purified final product.[134]

Dosage of amniotic membrane derivative drops

The frequency of AMED instillation ranges from once an hour to twice a day, with more frequent use recommended for indications such as chemical burns and wound healing disorders.[6] Baradaran *et al*. used a concentration of 0.5 mg/mL, though concentrations ranging from 0.1 to 1 mg/mL have been shown to effectively promote limbal stem cell proliferation.[135,140] Studies on processed HAF have typically involved instillation four times a day for short durations, usually around one week.[134]

Outcomes

AMED has been effectively used to treat a range of ocular surface conditions, including dry eye, neurotrophic keratopathy, delayed epithelial healing, chemical burns, and post-photorefractive keratectomy (PRK) recovery [Table 6]. In cases of delayed healing, complete epithelization is achieved in most cases with treatment durations ranging from 4 weeks to 7 months.[136,137,141,142]

For dry eye, AMEED has shown improvements in both symptoms and signs in more than 80% of patients, though longer treatment may be required for chronic cases.[137,141,143] In chemical injuries, AMED promotes faster healing in acute cases; in chronic injuries while it may reduce the size of the defect, complete healing may not be achieved.[144] It also aids in faster epithelial recovery in post-PRK patients and supplements *in vivo* limbal stem cell cultivation in autologous stem cell transplantation, leading to quicker epithelialization compared to conventional treatments.[135,140,145] Processed HAF has been studied to evaluate its impact on epithelial healing following corneal surface ablation and in patients with severe dry eye. Short-term treatment (1 week) of severe dry eye patients with processed AF (FloGraft, Applied Biologics Scottsdale, AZ USA) mixed in artificial tears and contact lenses soaked in the AF was found to improve symptoms and corneal staining in about 50% of the patients.[146] In patients undergoing PRK, processed AF

Table 5: Preparation of amniotic membrane extract drops

AMED preparation	Method of preparation
AMED prepared using Cryopreserved AM	
Baradaran-Rafii A *et al*.[135]	AM is washed with normal saline containing antibiotics, sliced into small pieces, and immersed in liquid nitrogen. The pieces are ground and mixed with distilled water in a 1:2 ratio, homogenized (20% duty cycle for 10 mins), and centrifuged at 4,000 g for 10 min at 4°C. The supernatant is centrifuged at 15,000 g for 5 min at 4°C and sterilized by passage through a 0.25 mm filter. AMED is applied at a concentration of 0.5 mg/mL.
Bonci *et al*.[136]	A 2 cm^2 patch of cryopreserved amniotic membrane is homogenized with 5 cc of balanced salt solution and 1 cc of antibiotic solution. The suspension is stored at −20°C for later use.
Lyophilized AMED[137]	Fresh amniotic membrane is washed with saline, decontaminated with antibiotics, and frozen in liquid nitrogen. Frozen amniotic membrane is ground and centrifuged at 4,500 rpm at room temperature. The supernatant is aliquoted into 1 mL vials, lyophilized, and stored at room temperature. The lyophilized AMED is reconstituted in 4 mL of sterile water before use and discarded after 15 days.

AMED – amniotic membrane extract drops

Table 6: Clinical outcomes of amniotic membrane extract drops in ocular surface disorders

Indication	Treatment duration, posology	Outcomes
Delayed epithelial healing[136,137,141,142]	Duration – 4 weeks to 7 months	Complete epithelialization is achieved in most cases within 4 weeks of treatment
Dry eye[137,141,143]	Duration – 4 weeks – 28 months Frequency – 2–8 times/day	Improvement in subjective symptoms and signs in about 89% of cases Improvements were observed after 4 weeks; continued to progress through to 12 weeks Longer treatment durations (up to 10 months) are required in chronic dry eye cases
Chemical injury[144]	Duration – weeks Frequency – 1–2 hourly	Healing of all acute cases, reduction in defect size to 58% in chronic cases.
Trans-PRK epithelial healing[145]	Duration – 3 days Frequency – 6 times/day	AMED accelerates epithelial healing, reduces congestion and pain, and results in less haze compared to the use of artificial tears
Limbal stem cell transplantation[135]	Duration – 2–3 weeks Frequency – 4–8 times/day	Complete epithelialization was achieved within 2–3 weeks in eyes treated with supplemental AMED; all cases receiving conventional treatment developed a persistent epithelial defect Corneal/conjunctival vascularization regressed dramatically 2–3 months after surgery

AMED – amniotic membrane extract drops; PRK – photorefractive keratectomy

offered a mild advantage in terms of uncorrected visual acuity and corneal irregularity at 1 month; however, this was not sustained, and all outcome measures were comparable with that of the conventional treatment group on later follow-ups.

Adverse Effects – Reported adverse effects with AMED are infrequent and include non-significant symptoms such as burning sensation, ocular discomfort, and irritation.[134,141,143,147] No major adverse effects have been reported with AF treatment till now.

Ocular Surface Immunoglobulin

Recent studies suggest that dry eye disease involves self-antigen-driven autoimmune inflammation, in addition to the conventional T-cell mediated pathway. Elevated IgG levels have been found in the tear fluid of dry eye patients, contrasting with the IgA predominance in healthy tear films. Furthermore, neutrophil-derived products, such as extracellular traps (NETs) and citrullinated proteins, as well as anti-citrullinated protein antibodies (ACPAs), are elevated in the ocular surface washings of dry eye patients. These ACPAs contribute to chronic inflammation. Ocular surface immunoglobulin (OSIG) has shown the potential to reduce this autoimmune inflammation.[7] OSIG has immunomodulatory activity that can potentially reduce this autoimmune-mediated inflammation.

Mechanism of action

OSIG is hypothesized to exert its effects through multiple pathways, modulating immune responses on the ocular surface to reduce inflammation and autoimmunity in dry eye disease. Autoantibody receptors on dendritic cells and neutrophils of the ocular surface can trigger immune responses. OSIG may block these receptors, limiting the harmful effects of autoantibodies. It contains anti-idiotypic antibodies that neutralize autoantibodies and reduce their production by binding to autoreactive B lymphocytes. Additionally, OSIG neutralizes ACPAs and inhibits NET formation. Other proposed mechanisms include complement inhibition, cytokine modulation, dendritic cell-mediated T-cell activation inhibition, and the expansion of regulatory T-cells.[7]

Preparation

OSIG is prepared by diluting commercially available intravenous immunoglobulins (IVIG) like flebogamma

DIF 5% in saline to a 0.4% concentration. This formulation is stable at room temperature for up to 2 years. Unlike commercially available pooled human IVIG, which does not require specialized compounding, autologous or allogeneic serum preparations—while essentially physiological IgG formulations—have a shorter shelf life and need to be prepared in specialized compounding pharmacies. Moreover, pooled human OSIG contains anti-idiotypic antibodies against human autoantibodies, which may exert an immunosuppressive effect in autoimmune diseases. However, anti-idiotypic antibodies are rarely found in IgG prepared from individual normal donors, implying that while IVIG eye drops contain anti-idiotypic antibodies, serum eye drops do not.[7]

Dosage

The topical application of IVIG is expected to achieve a higher concentration on the ocular surface. Studies have used a 0.4% (4 mg/mL) concentration of IVIG, based on the assumption that it provides a similar amount of IVIG as 50% AS eye drops.[7]

Outcomes

OSIG has emerged as a promising addition to the topical biological therapy arsenal for DED. A pilot study evaluating its outcomes in dry eye patients, including oGVHD and autoimmune dry eye disease, found that 0.4% OSIG significantly improved ocular surface staining, symptom scores, and tear inflammatory mediators after 8 weeks compared to a vehicle treatment.[7]

Adverse Effects: *In vitro* and animal studies have shown that 0.4% OSIG formulation is safe for topical use. The human study also reported no significant adverse effects, though the potential for infectious agent transmission remains, as IVIG is derived from pooled human plasma.[7]

Our Experience

We evaluated the use of topical autologous PL drops as an adjunct therapy for refractory dry eye disease in chronic ocular GVHD patients. Cases with dry eyes diagnosed within six months of chronic ocular GVHD, responded quickly to treatment, with improvement seen within 30 days. By six months, 75% of eyes achieved the least severity grading of dry eyes, and 75% no longer required topical steroids. There was a significant reduction in hyperemia, with 87.5% of participants showing symptomatic improvement. Ocular surface measures, including tear break-up time (TBUT), Schirmer's test, and staining scores, improved by six months. Tear analysis showed no significant changes in total protein and MMP-9 levels post-treatment.

We also evaluated the use of topical OSIG to treat various causes of dry eye disease, including ocular GVHD, autoimmune dry eye, meibomian, and SJS over a 12-month period. We observed significant improvements in symptom scores and ocular surface staining at 3 months, sustained up to 12 months. In comparison, the control group showed some improvement at 6 months, but the results were less pronounced. Both groups exhibited reduced conjunctival hyperemia, TBUT, and dry eye severity scores, but the improvements were more significant in the OSIG-treated group. Additionally, OSIG treatment led to a reduced need for topical lubricants and steroids. Only a few complications were noted, including anterior uveitis and microbial keratitis; however, these were unrelated to OSIG use, as cultures confirmed no contamination in the OSIG preparation.

Future Directions

Ocular surface disease treatment is shifting toward advanced biologics and recombinant drugs. One promising example is cenergermin, a recombinant form of NGF, which has shown efficacy in treating neurotrophic keratitis.[148] In addition to established therapies, newer drugs are on the horizon that could further revolutionize treatment paradigms. Emerging treatments such as tanafaercept, a TNF-α inhibitor, and topical anakinra, an IL-1 antagonist, were found to reduce inflammation and improve ocular surface health.[149] Furthermore, human recombinant HGF and CSB-001 have shown promise in enhancing epithelial regeneration and improving ocular surface healing.[150] As these innovative therapies continue to undergo clinical trials, they hold the potential to significantly improve patient outcomes, particularly for those with chronic or refractory ocular conditions. The integration of these new biologics into clinical practice will likely provide more targeted, effective treatments, shifting the paradigm toward more personalized, regenerative approaches for managing ocular surface disorders.

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