Umbilical Cord Blood and Serum for the Treatment of Ocular Diseases: A Comprehensive Review

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ABSTRACT

Several blood derivatives have been proposed for the treatment of various ocular diseases that affect either the anterior or the posterior segment of the eye. Blood sources may range from the patient’s own peripheral blood (autologous) to donor tissues, mainly allogeneic peripheral blood and umbilical cord blood (UCB). The utilization of the latter permits the collection of a large amount of serum all at once, and is characterized by therapeutic feasibility in patients with a poor general condition or anemia and blood dyscrasia. Products derived from UCB have two potential uses. First, serum in the form of eye drops can be applied topically onto the ocular surface to efficiently treat anterior segment disorders such as dry eye syndrome or corneal epithelial defects with different etiologies. The rationale for and efficacy of this application derive from the high concentrations of biologically active components and growth factors in UCB, which can nourish the ocular surface. Second, UCB is a source of stem cells, which are used in the field of regenerative medicine because they differentiate into various mature cells, including corneal and retinal cells. Therefore, UCB-derived stem cells have been proposed as a replacement therapy for the treatment of retinal and optic nerve diseases, given that current standard treatments often fail. The present review explores the clinical results that have been obtained using UCB-derived products in the field of ophthalmology, as well as the current limitations of those products in this field. Furthermore, given the promising development of UCB-based therapies, possible future directions in this area are discussed.

Keywords: Allogeneic serum; Cornea; Ocular surface disease; Optic nerve; Retina; Stem cells; Umbilical cord blood; Umbilical cord blood serum
The use of umbilical cord blood (UCB) derivatives for the treatment of ocular diseases has become increasingly popular in recent years. These derivatives include serum-based eye drops for the treatment of ocular surface disorders and stem-cell-based products for regenerating injured corneal, retinal, and optic nerve tissues. Studies evaluating the use of UCB-derived stem cells in human models are required. There is a need for a standardized therapeutic protocol that specifies the optimal formulation, dilution, and treatment duration for serum eye drops derived from UCB.

INTRODUCTION

Whole blood and various derivatives of it are used to treat a wide range of ophthalmic diseases that affect the ocular surface, the retina, and the optic nerve. Blood for ophthalmic clinical use can be extracted from the patient’s own peripheral blood (autologous blood) or from donors (allogeneic peripheral blood or umbilical cord blood, UCB). The most widely used blood-derivative products are fibrin-based products, albumin, serum, cryoprecipitate, platelets, plasmin, and fresh frozen plasma. Among platelet products, platelet-rich plasma (PRP) has a high concentration of essential growth factors and cell adhesion molecules, which is achieved by concentrating platelets into a small volume of plasma. PRP is applied as eye drops or clots to aid wound healing by enhancing the physiological process at the site of an injury [1].

The ocular application of blood and its derivatives ranges from instillation to the ocular surface in the form of eye drops (e.g., serum) to the use of whole blood on the retina during vitreoretinal surgery. The idea of using products derived from blood to treat ocular disease was first described over 40 years ago by Ralph and coauthors, who developed a mobile ocular perfusion pump to deliver autologous serum (AS) to the ocular surfaces of patients affected by chemical burns [2]. Since then, the application of eye drops derived from AS (UCB serum, UCBS) or allogeneic serum (allo-S) to treat a wide range of ocular surface diseases, mainly severe dry eye due to either Sjögren syndrome (SS) or ocular graft-versus-host disease (oGVHD), has been explored [3–7]. More recently, stem cells obtained from different sources, including UCB, have been used in cell replacement therapies for a variety of ocular pathologies (ranging from corneal scar to optic nerve degeneration) that are traditionally characterized by poor outcomes when treated with conventional therapies [8–17]. In the present review, we summarize the various types of products obtained from UCB and their current indications for the treatment of ocular diseases.

LITERATURE REVIEW: METHODS

In this review article, a systematic computerized search of the literature was conducted from inception until November 2019. All English-language articles dealing with the topic of UCB derivatives in the treatment of ocular diseases were retrieved from the electronic databases PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trials and then checked for applicability by the authors. The searches were performed by two independent investigators (G.G. and C.S.). The following keywords and MeSH terms were used: ‘allogeneic serum,’ ‘cornea,’ ‘ocular surface disease,’ ‘optic nerve,’ ‘retina,’ ‘stem cells,’ ‘umbilical cord blood,’ and ‘umbilical cord blood serum.’ All pertinent articles were thoroughly assessed, and their reference lists were scrutinized to identify any other studies that were applicable to this review. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.
UCB

The main application of UCB is hematopoietic stem cell (HSC) transplantation for the treatment of a variety of malignant and benign hematological disorders. The Center for International Blood and Marrow Transplant Research reported that over 8000 allogeneic transplant procedures were performed in the US in 2016 [18]. However, it is noteworthy that besides being a rich source of HSCs and hematopoietic progenitor cells, UCB is also a source of other cells with broad-ranging proliferation and differentiation capacities. These include mesenchymal stromal cells, capable of producing cells of the osteogenic, adipogenic, and chondrogenic lineages, and unrestricted somatic stem cells, a primitive cell type that expresses some features of pluripotent embryonic stem cells. Stem cells are undifferentiated cells that are defined by their ability to self-renew and differentiate into mature cells. They are attractive because of their high proliferative capacity, implying that an inexhaustible number of mature cells can be generated from a given stem cell source. Thus, cell replacement therapy has been proposed in recent years as a viable alternative treatment for various retinal pathologies, especially Stargardt’s disease, retinitis pigmentosa, and age-related macular degeneration (AMD). An effective treatment of AMD is of particular importance since it is a leading cause of irreversible vision loss among the elderly. Although the pathogenesis of AMD is yet to be fully elucidated, there is increasing evidence of the involvement of retinal pigment epithelium (RPE) cells, which are known to play a key role in promoting and supporting photoreceptor cell survival. As a result, dysfunction and loss of RPE cells can lead to photoreceptor degeneration and subsequent decreased vision. Stem cell therapy that represents a combined rescue and cell replacement strategy has been proposed as a means to manage vision-threatening complications of AMD. Additionally, RPE cells derived from stem cells are able to produce neurotrophic factors that support photoreceptor survival through the paracrine effect. Koh et al. investigated whether treatment with cells derived from human umbilical tissue was able to preserve photoreceptors and synaptic connectivity in a rat model of retinal degeneration caused by Mertk loss of function. Subretinal transplantation of cells derived from umbilical tissue was shown to rescue visual function by preserving retinal synaptic connectivity and attenuating glial reactivity. Multiple injections provided enhanced effects, thus confirming the potential therapeutic application of these cells in the setting of human retinal degeneration [19]. Recently, ischemic retinopathies such as diabetic retinopathy, retinopathy of prematurity, and retinal vein occlusion have been treated using vasoregenerative cell therapy [20–24]. Furthermore, cell therapy has emerged as a promising tool for optic nerve regeneration and is expected to fill current gaps in the field of optic nerve protection. Zhang and coauthors evaluated the effects of intravitreal injection of neural stem cells originating from UCB-derived mesenchymal cells on neurodegeneration in diabetic retinopathy in rats. The treated group exhibited attenuated vascular dysfunction 4 weeks following the transplantation procedure and increased levels of brain-derived neurotrophic factor (BDNF) compared to untreated rats. Moreover, morphologic retinal improvements were accompanied by signs of improved vision, as documented by flash electroretinogram. Several studies have since been conducted to evaluate the efficacy of UCB-based therapy in treating optic nerve injury with various etiologies. Chung and coauthors detected increased axon survival rates and decreased ganglion cell apoptosis in a model of optic nerve crush injury following a single intravitreal injection, whereas Zhang and Lv pointed out the positive effect of UCB treatment on optic nerve biomechanical properties, as shown by the increased maximum load, stress, and strain and the greater elasticity [8, 12, 13]. Furthermore, Ji and coauthors investigated the potential therapeutic benefits of intravitreally transplanted UCB-derived mesenchymal stem cells in an animal model of elevated intraocular pressure, which is a well-known risk factor for both the onset and progression of glaucomatous optic nerve damage. The transplantation procedure revealed a neuroprotective effect that...
| Study (year) | Design | Condition | Population (n) | Treatment | Control arm | Route | Frequency | Results |
|-------------|--------|-----------|----------------|-----------|-------------|-------|-----------|---------|
| Zhu (2011)  | Prospective comparative randomized | Traumatic optic neuropathy | Mice (48) | hUCB-MSCs | Injured-only group, neurotrophic factor-treated group, and group treated with neurotrophic factor plus hUCB-MSCs | Intravitreal | Single injection | Significant improvement in fVEP testing in treated groups compared with nontreated group. hUCB and neurotrophic factor mixture achieved the best results |
| Zhao (2011) | Prospective comparative randomized | ON injury | Mice (135) | hUCB-MSCs | Sham surgery group and unmanipulated mice receiving physiological saline solution | Intravitreal | Single injection | Increased RGC density, increased BDNF and GDNF mRNA expression, and improvement in pathological retinal changes in the hUCB-MSCs-treated groups |
| Chen (2013) | Prospective comparative randomized | ON injury | Mice (132) | hUCB-MSCs | Phosphate-buffered saline | Intravitreal | Single injection | Decreased RGC apoptosis and increased RGC survival in the early phase following treatment. Beneficial effect declined over time |
| Jiang (2013) | Prospective comparative randomized | Traumatic optic neuropathy | Mice (195) | hUCB-MSCs | Sham treatment | Intravitreal | Single injection | Ameliorated fVEP testing; increased RGC count and decreased RGC apoptosis |
| Zhang (2015) | Prospective comparative randomized | ON injury | Rabbit (48) | hUCB-MSCs | Sham treatment | Intravitreal | Single injection | Decreased ultrastructural ON damage; improved biomechanical properties (increased maximum load, maximum stress, maximum strain, elastic limit load, elastic limit stress, and elastic limit strain) of ON |
| Shao (2015) | Prospective comparative | Corneal endothelium deficiency | Rabbit (16) | hUCB-EPCs labeled with CD34 immunomagnetic nanoparticles without a magnet; EDM stripping without injection of cells; unmanipulated rabbits | CD34 immunomagnetic nanoparticle-labeled UCB EPCS | Intracameral injection plus magnetic attraction (cells migrate directionally) | Single injection | Treated corneas became relatively transparent, with little edema |
| Lv (2016) | Prospective comparative randomized | ON injury | Rabbit (60) | hUCB-MSCs | Intravitreal BDNF | Single injection | Recovery of viscoelasticity of ON (increased stress relaxation and creep properties) in treated groups |
| Chung (2016) | Prospective comparative | ON crush | Mice (90) | hUCB-MSCs | Sham treatment | Intraarterial | Single injection | Increased axon survival rates, increased visual function (GAP-43 upregulation), and increased oxygen availability (HIF-1α upregulation) |
| Wang (2016) | Prospective comparative randomized | Oxygen-induced retinopathy | Mice (7) | hUCB-MSCs | Unmanipulated mice; phosphate-buffered saline-treated group. | Intravitreal | Single injection | Faster recovery from retinopathy and lower number of neovascular nuclei in UCB-MSCs-treated group |
| Study (year) | Design | Condition | Population (n) | Treatment | Control arm | Route | Frequency | Results |
|-------------|--------|-----------|----------------|-----------|-------------|-------|-----------|---------|
| Zhang (2017) [9] | Prospective comparative randomized | Diabetic retinopathy | Mice (-) | hUCB-MSCs | Sham treatment | Intravitreal | Single injection | 0.2 x 10⁶ cells in 2 μL. Attenuation of retinal vascular dysfunction, BDNF and Thy-1 upregulation; decreased retinal vessel leakage; better visual function based on positive ERG testing |
| Mohamed (2017) [22] | Prospective comparative | Cryo-induced retinal injury | Mice (48) | hUCB-MSCs | Unmanipulated mice; intravenously treated group | Intravitreal vs intravenous injection | Single injection | Near-normal retinal structure in MSCs-treated group. Modulation of oxidant-apoptotic status: increased expression of Bcl-2, HMOX1, TXN2; downregulation of 3-NT and caspase-3. Increased bFGF |
| Dong (2017) [23] | Prospective comparative randomized | Diabetic retinopathy | Mice (60) | hUCB-MSCs | 2 μL phosphate-buffered saline | Intravitreal 2 μL | Single injection | Comparable beneficial effects of intravitreal and intravascular administration routes on vascular repair. Fewer human cells observed in the retinal vasculature following systemic delivery |
| Reid (2017) [20] | Prospective interventional comparative | Oxygen-induced retinopathy | Mice (-) | hUCB-MSCs | Unmanipulated mice | Intravitreal vs intraarterial | Single injection | Ameliorated retinal layer structure; reduced retinal vessel leakage |
| He (2018) [21] | Prospective comparative | Retinal laser injury | Mice (-) | hUCB-MSCs | Sham treatment | Intravitreal 5 μL PBS alone, MSCs-Exos at a concentration of 50 μg/mL, and different concentrations of exosomes (Exo-L: 25 μg/mL, Exo-M: 50 μg/mL, and Exo-H: 75 μg/mL) for 8, 16, and 24 h | Single injection | Downregulated expression of VEGF mRNA in RPE cells induced by MSC-derived exosomes in vivo and ex vivo after blue light stimulation; subsequent CNV reduction and ameliorated visual function |
| Ji (2018) [25] | Prospective comparative randomized | Ocular hypertension | Mice (54) | hUCB-MSCs | Unmanipulated mice; phosphate-buffered saline-treated group | Intravitreal | Single injection | Increased numbers of RGCs and axons and increased expression of GDNF and BDNF in hUCB-MSCs-treated groups |
| Koh (2018) [19] | Prospective interventional comparative | Retinal degeneration | Mice (-) | hUCB-MSCs plus steroids and cyclosporine A | Unmanipulated mice | Subretinal | Single or double injection | Preserved retinal synaptic connectivity and decreased Müller glial cell reactivity |
could be related to the secretion of trophic factors such as BDNF and glial cell-derived neurotrophic factor [19, 24, 25]. Table 1 summarizes the main published studies on UCB use in ophthalmic practice.

UCBS

Serum is the noncellular supernatant that is left when whole blood clots. The rationale for applying serum to the ocular surface is that, compared to conventional lubricant treatments, it more closely resembles natural tears due to several of its biochemical constituents [3]. UCBS has been extensively used in the setting of ocular surface diseases and has produced satisfactory results in terms of efficacy and safety [3, 26–43]. Yoon and coauthors were among the first to test the use of UCBS in the management of several ocular surface disorders, such as dry eye with or without SS, oGVHD, persistent epithelial defects, neurotrophic keratitis, and ocular chemical injury. Serum eye drops were administered topically 6–10 times a day over a period ranging from 2 to 6 months. Treated patients showed a faster epithelial healing rate, greater improvement in symptoms, and increased goblet cell density and corneal sensitivity when compared to healthy subjects. In particular, patients with neurotrophic keratitis experienced a 100% healing rate after approximately 1 month of therapy [26–33]. Furthermore, a significant improvement in corneal epitheliopathy (as indicated by a decreased Oxford staining score) and a higher number of nerves with improved morphology and lower tortuosity were reported by our group, who successfully treated moderate-to-severe forms of dry eye disease with UCBS [6]. Furthermore, the efficacy of serum-based therapy was measured objectively as the decreased expression of inflammatory markers such as cytokines and growth factors via histological examination in mouse models [34, 35]. A recent randomized crossover clinical trial compared the efficacy of UCBS and peripheral adult donor blood serum in the treatment of severe dry eye. Overall, signs improved after either treatment, but the UCBS treatment was found to be

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Table 1 continued

| Study | Design | Condition | Population | Treatment | Route | Control arm | Results |
|-------|--------|-----------|------------|-----------|-------|-------------|---------|
| Huang (2019) | Prospective comparative | ON crush | Mice (10) | UCB human umbilical cord blood, MSCs | Single intravitreal injection | 2D-MSCs had stronger promoting effect than 3D-MSCs on RGC survival and ON axonal regeneration. Improved IOP and sustained secretion of regeneration-stimulating factors (SCGF-β, HGF, MCP-1, IL-8, and SDF-1α). | 2D-MSCs induced the activation of key neuroprotection pathways (JAK/STAT3 and MAPK/ERK). |

UCB, umbilical cord blood; ON, optic nerve; RGC, retinal ganglion cell; 2D-MSCs, 2D mesenchymal stem cells; 3D-MSCs, 3D mesenchymal stem cells; SCGF-β, stem cell growth factor-β; HGF, hepatocyte growth factor; MCP-1, monocyte chemoattractant protein-1; IL-8, interleukin-8; SDF-1α, stromal cell-derived factor-1α; FGF, fibroblast growth factor; RPE, retinal pigment epithelium; CNV, corneal neovascularization; Bcl-2, B cell lymphoma (Bcl)-2 gene; HMOX, heme oxygenase; TXN, thioredoxin; 3-NT, 3-nitrotyrosine; bFGF, basic fibroblast growth factor; HIF-1α, hypoxia-inducible factor-1α; HGF, hepatocyte growth factor; EPC, endothelial progenitor cell; EDMM, endothelial-Descemet membrane layer; GDNF, glial cell line-derived neurotrophic factor.
superior in terms of ameliorating subjective symptoms and reducing corneal damage [44].

The potential useful role of serum-based therapy is not limited to ocular surface diseases; it extends to neurodegenerative disorders such as glaucoma. A preliminary study that analyzed the effect of UCBS topically administered to glaucoma patients observed positive results, as shown by improvements in visual field test parameters. This efficacy is thought to be related to the high growth factor content of the serum, which potentially exerts a neuroprotective action on the optic nerve [45]. However, the authors stated that the incidentally observed amelioration in these glaucoma patients requires further investigation.

The main advantages of using serum eye drops obtained from donors such as UCBS are related to the elimination of the proinflammatory cytokines and autoantibodies present in the sera of patients with dry eye caused by systemic diseases (e.g., SS and oGVHD), as those proinflammatory cytokines and autoantibodies could cause damage if applied to the ocular surface [6]. This aspect should theoretically discourage the use of AS in these patients, who represent a significant percentage of severe dry eye cases. However, a recent study showed positive effects of AS on both the subjective symptoms and the objective signs of dry eye caused by systemic autoimmune diseases [46]. In another study, an attempt to predict the quality of AS by categorizing patients with SS into active and inactive groups according to the clinical activity of the disease failed to show any significant difference in therapeutic effect between the two groups [47]. Therefore, additional evidence is needed to clarify whether the use of AS can also be advantageous in patients with concomitant systemic diseases. Other advantages include the ability to use these products in patients with poor venous access, anaemia, and blood dyscrasia, and the potential to create a pool with the desired content of each growth factor. In fact, there is marked interindividual variability in growth factor content, which is thought to be the consequence of a combination of genetic, clinical, and pharmacological factors [48, 49]. Therefore, in order to reduce the variability in the biological constituents of the serum, pooling of serum samples from multiple donors is implemented to obtain final serum products containing required levels of the main constituents. This can be achieved in the laboratory by dosing serum with the desired growth factor, but such a procedure is expensive. Recently, preselection of UCBS with the ideal concentration of epidermal growth factor was realized by collecting UC samples from young mothers (< 30 years) with a high CD34+ cell content (0.05 × 10^6/mL) following a long labor (> 6 h) [50]. The same approach could be applied to the other growth factors that play a pivotal role in ocular surface homeostasis (e.g., nerve growth factor).

The main disadvantage of allogeneic serum eye drops is the risk of transmitting infections, so it is essential to produce the serum according to good manufacturing practices. There are controversial theories concerning the need for ABO matching between donor and recipient. On the one hand, it is known that serum contains high levels of ABO substances that might act as antigens and initiate immune-complex-mediated inflammation. On the other hand, the sporadic clinical use of ABO-mismatched eye drops has not been associated with overt immune-complex-mediated hypersensitivity. Table 2 summarizes the main published studies on the use of UCBS in ophthalmic practice.

The frequency and duration of treatment depends upon individual circumstances and are not governed by evidence-based guidelines. The Royal College of Ophthalmologists recently provided two examples of protocols for serum-derived eye drops: (1) withdrawal of treatment after 1 year of therapy in patients with ocular surface disease to define induction of remission, before reinstating indefinite treatment if the symptoms relapse; (2) withdrawal of treatment after the ocular surface has healed in patients with persistent corneal epithelial defects, with treatment restored only if the surface shows signs of recurrence. Recently, a research group summarized the current unanswered questions in this field and termed them the 5 W’s and 2 H’s: Who is the patient? Why is a blood-based treatment needed? When is it appropriate? Where are products dispensed? What is the product of choice? How is the product...
| Study (year) | Design | Condition | Population | Control arm | Frequency (duration) | Concomitant therapy | Results |
|-------------|--------|-----------|------------|-------------|---------------------|---------------------|---------|
| Vajpayee (2003) [39] | Prospective randomized double-blind | PED | Human (59) | Autologous serum | 6/day (21 days) | – | Higher percentage of reepithelization in UCBS group |
| Yoon (2005) [29] | Prospective interventional | PED | Human (14) | – | 6/day (until healing) | – | Faster epitheliopathy healing rate |
| Yoon (2007) [27] | Prospective interventional | NK | Human (28) | – | 6–10/day (until healing) | Tear substitutes, levoﬂoxacin | 100% healing within 4.4 weeks on average |
| Yoon (2007) [28] | Prospective interventional comparative | Dry eye | Human (48) | Autologous serum | 6–10/day (2 months) | Tear substitutes | Major improvements in symptoms, keratoepitheliopathy score, and goblet cell density in hUCBS-treated group |
| Yoon (2007) [30] | Prospective interventional noncomparative | GVHD | Human (12) | – | 6–10/day (6 months) | Tear substitutes | Significant improvements in symptoms, corneal sensitivity, TBUT, and keratoepitheliopathy scores |
| Sharma (2011) [40] | Prospective randomized double-blind | Chemical injury | Human (32) | Autologous serum/tear substitutes | 10/day (3 months) | Ofloxacin, prednisolone acetate, homatropine hydrobromide, sodium citrate, ascorbate, tear substitutes | Higher percentage of corneal transparency in UCBS group |
| Study (year)          | Design                                      | Condition     | Population (n) | Control arm | Frequency (duration) | Concomitant therapy                                                                 | Results                                                                                                                                 |
|----------------------|---------------------------------------------|---------------|----------------|-------------|----------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Oh (2012) [35]       | Prospective interventional comparative      | Chemical injury | Mice (24)      | hPBS, tear substitutes | 4/day (–)            | Levofloxacin                                                                       | Lower ED parameters, haze scores, stromal inflammation, edema, and IL-1β levels in hUCBS group                                           |
| Yoon (2013) [32]     | Prospective interventional comparative      | Post-LASEK PED | Human (60)     | Conventional therapy | 4–6/day (–)          | Conventional therapy (antibiotics, steroid, and artificial tear eyedrops)         | Longer TBUT and lower keratoepitheliopathy and TGF-β1 levels in hUCBS-treated group                                                   |
| Versura (2013) [42]  | Prospective interventional                  | PED           | Human (30)     | –           | 8/day (1 month)      | –                                                                                 | Significant reduction in epithelial damage                                                                                           |
| Erdem (2014) [41]    | Prospective interventional                  | PED           | Human (14)     | –           | 5–10/day (21 days)   | Tear substitutes, lomefloxacin                                                   | 75% healing within 12 days                                                                                                          |
| Mukhopadhyay (2015) [7]| Prospective interventional comparative      | Dry eye       | Human (144)    | Autologous serum, tear substitutes | 6/day (6 weeks)      | –                                                                                 | Significant improvements in clinical parameters and tear protein profile (lysozyme and lactoferrin upregulation, sustained increase in total tear protein level) in serum-treated groups |
| Study (year)          | Design                                      | Condition                                      | Population | Control arm | Frequency (duration) | Concomitant therapy | Results                                                                                   |
|----------------------|---------------------------------------------|-----------------------------------------------|------------|-------------|----------------------|---------------------|-------------------------------------------------------------------------------------------|
| Giannaccare (2017)   | Prospective interventional open-label       | cGVHD, Sjögren syndrome, diabetic keratopathy, neurotrophic keratitis | Human (20) | –           | 8/day (2 months)     | –                   | Significant decreases in OSDI, VAS, and Oxford grading values. Significant increases in corneal sensitivity, ST, and BUT scores. Higher total number of nerves as well as improved morphology and lower tortuosity. Presence of neuromas and higher dendritic cell density at baseline associated with greater reduction in OSDI after treatment |
| Kamble (2017)        | Prospective interventional comparative randomized | Post-keratoplasty PED | Human (105) | Autologous serum, tear substitutes | 6/day (until healing) | –                   | Decreased ED size and faster reepithelialization in serum-treated groups                  |
| Han (2019)           | Prospective interventional comparative randomized | Chemical injury | Mice (28) | hAM; hPBS; saline | 4/day (7 days) | –                   | Major decrease in epithelial defect areas in hUCBS group compared with hAM, hPBS, and saline groups. Reductions in degree of corneal opacity and inflammatory marker expression (TNF-α, IL-6, MMP-8, and MMP-9 mRNA) in all treatment groups |
CONCLUSIONS AND FUTURE DIRECTIONS

Umbilical cord tissue is a major source of stem cells, which can be efficiently used to treat several ophthalmic disorders. Therapeutic strategies based on stem cells depend not only on the synthesis of trophic and growth factors but also on the application of both mesenchymal and epithelial stem cells with anti-inflammatory and immune-privileged properties, as they can replace damaged tissues by differentiating into retinal and corneal epithelial, stromal, and endothelial cells. Several studies have evaluated the use of UCBS in experimental models of induced retinal and corneal injuries, but there are still no data on its application in humans [52]. Further clinical studies are needed to evaluate the effect and long-term safety of this therapy in human ophthalmic disorders, to clarify pharmacokinetic aspects, and to provide a standardized therapeutic scheme for the clinical use of UCBS. Future research should also focus on standardizing protocols for cell culture, differentiation, expansion, and cryopreservation, as well as optimizing cell culture media and scaffolds that can support cell proliferation, maintenance, and differentiation.

On the other hand, more robust evidence is available on the use of UCBS for the treatment of ocular surface diseases. In fact, various randomized controlled trials or laboratory analyses have addressed the therapeutic use of UCBS that need to not only assess UCBS efficacy and safety but also its clinical superiority to both autologous and allogeneic serum eye drops in terms of clinical efficacy and cost-effectiveness. Detailed analyses of the constituents of allogeneic serum are required to investigate the bioavailability among donations and the impact that this bioavailability could have on the therapeutic use of UCBS. Further clinical studies are needed to address these aspects and to provide a standardized therapeutic scheme for the clinical use of UCBS. Future research should also focus on standardizing protocols for cell culture, differentiation, expansion, and cryopreservation, as well as optimizing cell culture media and scaffolds that can support cell proliferation, maintenance, and differentiation.

Table 2 continued

| Study (year) | Design | Condition | Population (n) | Control arm | Frequency (duration) | Concomitant therapy | Results |
|--------------|--------|-----------|----------------|-------------|----------------------|---------------------|---------|
| Campos (2019) [44] | Multicenter, randomized, double-masked crossover clinical trial | Severe dry eye disease | Human (60) | Peripheral adult donor blood serum eye drops | 8/day (1 month) | – | Corneal staining was more significantly reduced after the CBS treatment. Reduced VAS and OSDI scores were observed in both groups |

UCBS umbilical cord blood serum, NK neurotrophic keratitis, PED persistent epithelial defect, RCE recurrent corneal erosion, hAM human amniotic membrane, hPBS human peripheral blood serum, cGVHD chronic graft-versus-host disease, OSDI Ocular Surface Disease Index, VAS Visual Analogue Scale, ST Schirmer’s test, TBUT tear break-up time, ED epithelial defect, LASEK laser epithelial keratomeileusis
have on the effectiveness of the final product. Further research is also required on the optimal formulation (type of vehicle), dilution (20% vs 50–100%), duration of treatment (one or more months), and timing of repeated cycles (fixed or individualized for each clinical case). Last but not least, the development and validation of specific tools for both patient-reported and objective outcomes as well as minimal clinical datasets for collecting, analyzing, and sharing data are required.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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