Original Article

Safety and efficacy of eye drops from umbilical cord blood platelet lysate to treat resistant corneal ulcer

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ABSTRACT

Background: Umbilical cord blood (UCB) is a novel treatment of resistant corneal ulcers owing to the unique anti-inflammatory molecules and growth factors it contains. Platelet lysates are a potential future alternative. The aim of the present study was to assess the role of human UCB platelet lysate in treating resistant corneal ulcers.

Methods: This was prospective, non-comparative, interventional case series involving 40 eyes of patients aged 6 – 65 years with persistent corneal ulcers from the Mansoura Ophthalmic Center and Mansoura Research Center for Cord Stem Cells. Patients were classified according to the cause of persistent corneal ulcer into four groups: group I, including 14 eyes with dry eye disease; group II, including six eyes post-keratoplasty; group III, including four eyes with corneal chemical burn; and group IV, including 16 eyes with persistent corneal ulcer from other causes. All participants underwent detailed ophthalmic examinations, and baseline and final best-corrected distance visual acuity (BCDVA) were recorded. Eye drops were prepared from UCB platelet lysate and administered to all patients along with detailed meticulous instructions for the method of use. Clinical progression of wound healing was continuously observed. The treatment response was identified as complete healing, improvement, or treatment failure.

Results: BCDVA improved significantly in all studied groups (all $P < 0.05$). In group I, complete healing, improvement, and treatment failure occurred in 71%, 29%, and 0% of cases. In group II, complete healing, improvement, and treatment failure occurred in 67%, 33%, and 0% of cases. In group III, complete healing, improvement, and treatment failure occurred in 50%, 50%, and 0% of cases. In group IV, complete healing, improvement, and treatment failure occurred in 63%, 12%, and 25% of cases. No adverse events associated with the treatment were observed or subjectively self-reports in the study period.

Conclusions: Eye drops from UCB platelet lysate were a novel therapeutic blood component with unique growth factors and anti-inflammatory compounds that could be an effective and safe treatment option in managing persistent corneal ulcers of different causes. A future randomized clinical trial with a large sample size and a longer follow-up is required to confirm these preliminary outcomes.

KEYWORDS

umbilical cord, umbilical cord blood, human platelets lysates, allogeneic, eyedrop, ophthalmic solution, treatment, ulcerative keratitis

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INTRODUCTION

Corneal ulcer is a corneal epithelium defect with / without the involvement of the surrounding stroma, which is an ocular emergency possibly affecting eyesight [1]. Corneal ulcers can arise from different causes, such as mechanical and chemical trauma, dry eye disease, neurotropic disorders, and corneal infections [2]. Persistent corneal epithelial defects (PEDs) and chronic corneal ulcers are challenging to heal and may result in vision loss due to inflammation, infection, corneal thinning, corneal scarring, opacification, and perforation [3]. Resistant corneal ulcers may result from failure of rapid healing within 14 days even with standard supportive treatment [4].

Corneal wound healing is mediated by growth factors, such as fibroblastic growth factors, epidermal growth factors (EGFs), and platelet-derived growth factors, which induce corneal epithelial cell migration, proliferation, and differentiation [5]. The rationale for utilizing platelets instead of other blood cells is that they serve as the repository for growth factors, cytokines, and alpha granules, which contain cell adhesion molecules. These substances, which are essential for the healing process, are generated when platelets are activated [6].

Platelet-rich plasma (PRP) includes growth factors and cytokines that may aid in re-epithelialization and maintain ocular surface health. It plays a vital function of supporting the healing process when used to treat a range of ocular surface disorders [7]. However, using a preparation of autologous PRP may not be feasible in patients with autoimmune disorders that are commonly associated with corneal ulcers because of the presence of circulating autoantibodies that may aggregate corneal inflammation and regress the healing process [8]. Moreover, the allogenic source should be considered in very young and elderly patients, who may have risks of recurrent autologous blood collection [9].

The use of derivatives of umbilical cord blood (UCB) that contains unique anti-inflammatory molecules and growth factors is a novel treatment option [10]. Umbilical cord tissue is a major source of stem cells, which can be efficiently used to treat several ocular disorders. The therapeutic properties of UCB serum-derived eye drops have been documented in a previous study [11]. The concentration of growth factors, such as EGFs and transforming growth factors, in UCB are two to three times higher than that in autologous blood derivatives [12]. UCB exerts a bacteriostatic effect owing to the anti-bacterial factors, such as immunoglobulin G, lysozyme, and complement, it contains. In addition, it contains neurotrophic factors that improve neurotrophic keratitis [13].

Platelet lysates obtained by recurrent freezing and thawing of platelet constituents are a potential future alternative [14]. Platelet components, whether autologous or allogeneic, may be transformed into platelet lysate by freeze-thawing. This method could be used to generate formulations comprising greater concentrations of growth factors compared to usual PRP eye drop solutions [15].

Therefore, the aim of the present study was to assess the role of eye drops from human UCB platelet lysate to treat resistant corneal ulcers.

METHODS

This was a prospective, non-comparative, interventional case series involving 40 eyes of patients aged 6 – 65 years with persistent corneal ulcers from the Mansoura Ophthalmic Center and Mansoura Research Center for Cord Stem Cells (MARC-CSC). The Institutional Review Board of Mansoura University, Faculty of Medicine, Mansoura, Egypt, approved the study protocol (approval code number: R.21.05.1338). The study was performed from June 2021 to June 2022. All study procedures were performed in accordance with the tenets of the Declaration of Helsinki by the World Medical Association. All adult patients provided written informed consent. Informed consent was obtained from parents or legal guardians of the children.

Patients were divided according to the cause of persistent corneal ulcer into four groups: group I, including 14 eyes with aqueous tear-deficient dry eye; group II, including six eyes post-keratoplasty (four eyes post-penetrating keratoplasty and two eyes post-deep anterior lamellar keratoplasty); group III, including four eyes with corneal chemical burn (three eyes with alkaline chemical burn and one eye with acidic chemical burn); and group IV, including 16 eyes with persistent corneal ulcer due to other causes, including post-fungal keratitis (*Aspergillus fumigatus* and *Candida albicans*), post-coronavirus disease (an episode of severe coronavirus disease and admission to the intensive care unit due to coronavirus disease-induced respiratory failure), post-cataract surgery, post-herpes simplex virus keratitis, limbal stem cell deficiency, corneal ulceration due to radiotherapy, and neurotrophic keratitis (Table 1). Recruited patients underwent complete ophthalmic examinations. A

persistent corneal ulcer was defined as a corneal epithelial defect with / without stromal defect persisting for at least 2 weeks without improvement in the size or depth despite standard treatment [16].

Cord blood (CB) units were collected at the Obstetric Unit of the Mansoura University Hospital. Prenatally, the mothers filled out a donor consent form authorizing the use of these samples for research and validation. The collection bag contained 22 mL of the citrate-phosphate-dextrose-adenine 1 (CPD-A1) anticoagulant (JMS CB bag, CPDA-1, JMS Singapore, Ltd.). Each processed CB unit was chosen according to the quality control criteria for the CB collection bag. The most common exclusion criterion was the presence of total nucleated cells < 1.5×10^6 /mL. The inclusion criteria for CB PRP were < 48 h after collection, > 70 mL volume (including CPD-A1), absence of visible hemolysis, and platelet concentration ≥ 150×10^6/mL [17, 18].

Full serologic testing of the CB bags was performed to exclude infection. Negative results were obtained for infectious disease indicators, such as hepatitis B and C viruses, human immunodeficiency virus, *Treponema pallidum* antibodies (syphilis), *Toxoplasma gondi*, and cytomegalovirus [19, 20].

CB units were collected at the Obstetric Unit of the Mansoura University Hospital. The mother's complete history-taking and physical examination were performed to exclude systemic and genetic disorders. CB was collected from a full-term delivery, with the absence of fever or premature rupture of membranes. Prenatally, the CB collection process was explained to the mothers. Postnatally, the umbilical cord was clamped toward the newborn's umbilicus, and the umbilical vein was cannulated to collect CB.

A total of 16 CB units were collected and transported to MARC-CSC at the Mansoura University. Under complete sterilization, each unit was transferred into a number of 15-mL falcon tubes according to the volume of the bag in class II laminar airflow (Angelantoni Life Science Industrie, Italy). All tubes were centrifuged at a low speed (200g; fixed-angle Thermo Fisher Scientific centrifuge) to separate PRP at a low speed (200g) for 10 min. The recovered supernatant comprised the PRP. The PRP was transferred into another 15-mL falcon tube to be centrifuged at a high speed (2000g) for 15 min to gain two fractions: platelet-poor plasma (PPP) and a platelet pellet suspended in PPP to obtain a CB-platelet concentrate (CB-PC) ranging from 600 to 1200×10^6 platelets/mL in 9 ± 3 mL. Subsequently, the fractions were stored at - 80°C. The CB-PC fraction was frozen in preparation for quarantine. Only CB-PC samples with negative serology outcomes were utilized to prepare cord blood platelet lysate (CBPL) [21].

CB-PC samples underwent three rounds of freeze (- 80°C) / thaw (37°C) cycles to lyse platelets and release growth factors, accompanied by centrifugation at a high speed (5000g) for approximately 15 min. The supernatant-rich growth factor and intact free platelets were aspirated and filtered through a 0.45-μm-pore syringe filter (Corning, NY 14831-001, USA). The used bottle was kept under refrigeration at + 4°C, while the remaining bottles were stored under refrigeration at - 20°C [21, 22].

Table 1. Baseline characteristics, etiology, best-corrected distance visual acuity, and treatment outcomes of study participants

Variables		Group 1 (n = 14)	Group 2 (n = 6)	Group 3 (n = 4)	Group 4 (n = 16)
Age (y), Mean ± SD		29.9 ± 14.1	29.3 ± 21.9	35.3 ± 20.6	32.7 ± 14.9
Sex (Male / Female), n %)		5 (36) / 9 (64)	2 (33) / 4 (67)	1 (25) / 3 (75)	6 (37) / 10 (63)
Affected eye (Right / Left), n (%)		8 (57) / 6 (43)	1 (17) / 5 (83)	2 (50) / 2(50)	9 (56) / 7 (44)
BCDVA (decimal), Mean ± SD	**Pre-treatment**	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.1	0.0 ± 0.0
	Post-treatment	0.4 ± 0.2	0.4 ± 0.2	0.2 ± 0.1	0.3 ± 0.2
	***P*-value**	**< 0.001**	**0.003**	**0.014**	**< 0.001**
Duration of complete healing (d), Mean ± SD		9.5 ± 3.2	13.0 ± 1.4	14.5 ± 0.7	11.7 ± 4.1
Outcome, n (%)	**Complete healing**	10 (71)	4 (67)	2 (50)	10 (63)
	Improvement	4 (29)	2 (33)	2(50)	2 (12)
	Treatment failure	0 (0)	0 (0)	0 (0)	4 (25)

Abbreviations: y, years; SD, standard deviation; n, number; %, percentage; BCDVA, best corrected distance visual acuity; d, days. *P*-values < 0.05 are shown in bold. Note: Etiology in each group, n (%): Group 1, dry eye = 14 (100%) eyes; Group 2, post-keratoplasty (graft ulcer) = 6 (100%) eyes; 4 (67%) eyes post-penetrating keratoplasty and 2 (33%) eyes post-deep anterior lamellar keratoplasty; Group 3, corneal chemical burn = 4 (100%) eyes; 3 (75%) eyes with alkaline chemical burn and 1 (35%) eye with acidic chemical burn; Group 4, post fungal keratitis = 2 (12.5%) eyes, post-coronavirus disease = 2 (12.5%) eyes, post-cataract surgery = 2 (12.5%) eyes, post-herpes simplex virus keratitis = 2 (12.5%) eyes, limbal stem cell deficiency = 4 (25%) eyes, corneal ulceration due to radiotherapy = 2 (12.5%) eyes, and neurotrophic keratitis = 2 (12.5%) eyes.

The corneal reflex was tested using a cotton-tipped applicator to determine the presence / absence of corneal sensitivity [23]. At each appointment, patients underwent a comprehensive ocular examination, including the measurement of best-corrected distance visual acuity (BCDVA) using a Snellen chart (CP 670 automatic chart projector; Nidek Co., Ltd., Gamagori, Japan) and expressed up to one decimal point, and slit-lamp biomicroscopy (Topcon SL-7F Slit Lamp - Alternup Medical, France). Intraocular pressure was measured using the Goldmann applanation tonometer Tono-Pen XL (Medtronic Solan, Jacksonville, FL, USA). Slit-lamp images were acquired at each visit. The greatest diameter of the corneal ulcer was measured along two perpendicular axes using a slit-lamp micrometer.

Patients were provided with three bottles of CBPL at each visit and instructed to store them in a domestic freezer. One bottle was thawed every day at room temperature for use on the same day. The thawed container was stored in a household refrigerator on the day of usage to prevent contamination and preserve the stability of growth factors. Patients were instructed to administer the eye drops 4 – 6 times throughout the day and check every 3 days for tolerance to treatment. Patients were followed-up daily for 1 week then weekly until epithelization was complete. Healing was defined as completion of epithelization accompanied by symptom alleviation at the last follow-up [24]. Improvement was defined as diminution in the corneal ulcer depth or size at the last follow-up. Treatment failure was defined as persistence of the ulcer with no improvement or reduction in the ulcer area for over 18 days [24]. Furthermore, we assessed complications, such as thinning, perforation, melting, calcifications, infections, and vascularization, before treatment initiation and at follow-up visits.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Inc., Armonk, NY, USA). Qualitative variables are expressed as frequency and percentage. The Shapiro – Wilk normality test and histograms of normality were used to test the distribution of quantitative variables to select the type of statistical testing. Quantitative variables were compared using paired Student's *t*-test and expressed as mean (standard deviation [SD]). Final and baseline BCDVA values were compared in each group. A two-tailed *P*-value < 0.05 was considered to indicate statistical significance.

RESULTS

All participants completed follow-up examinations. Table 1 shows the characteristic data of the study participants. In group 1, the mean (SD) duration of complete healing was 9.5 (3.2) days. BCDVA at the last follow-up showed significant improvement from baseline ($P < 0.001$). Complete healing, improvement, and treatment failure occurred in 71%, 29%, and 0% of cases (Table 1 and Figure 1).

In group 2, the mean (SD) duration of complete healing was 13.0 (1.4) days. BCDVA at the last follow-up showed significant improvement from baseline ($P < 0.05$). Complete healing, improvement, and treatment failure occurred in 67%, 33%, and 0% of cases (Table 1 and Figure 2).

In group 3, corneal thinning was observed in two (50%) eyes before treatment, and stromal thickness improved noticeably after complete healing on slit-lamp examination. The mean (SD) duration of complete healing was 14.5 (0.7) days. BCDVA at the last follow-up showed significant improvement from baseline ($P < 0.05$). Complete healing, improvement, and treatment failure occurred in 50%, 50%, and 0% of cases (Table 1 and Figure 3).

In group 4, corneal thinning was observed in three (19%) eyes before treatment, and stromal thickness improved noticeably after complete healing on slit-lamp examination. The mean (SD) duration of complete healing was 11.7 (4.1) days. BCDVA at the last follow-up showed significant improvement from baseline ($P < 0.001$). Complete healing, improvement, and treatment failure occurred in 63%, 12%, and 25% of cases (two eyes with limbal stem cell deficiency and two eyes with neurotrophic keratitis; Table 1 and Figure 4).

Clinical variables, such as corneal inflammation, conjunctivalization, corneal neovascularization, or pain, were not assessed individually. Nevertheless, pain and inflammation reduced markedly over time until complete healing in all cases.

Thinning was found in two eyes with chemical burn in group 3 (immediately at the time of chemical burn) and in three eyes with post-fungal keratitis in group 4 (at the start of presentation of fungal keratitis in two eyes and 2 weeks after treatment of fungal corneal abscess in one eye).

Throughout the study period, no adverse events associated with the treatment were found on examination or self-reported. None of the eyes underwent other interventions, such as tarsorrhaphy, at the follow-ups.

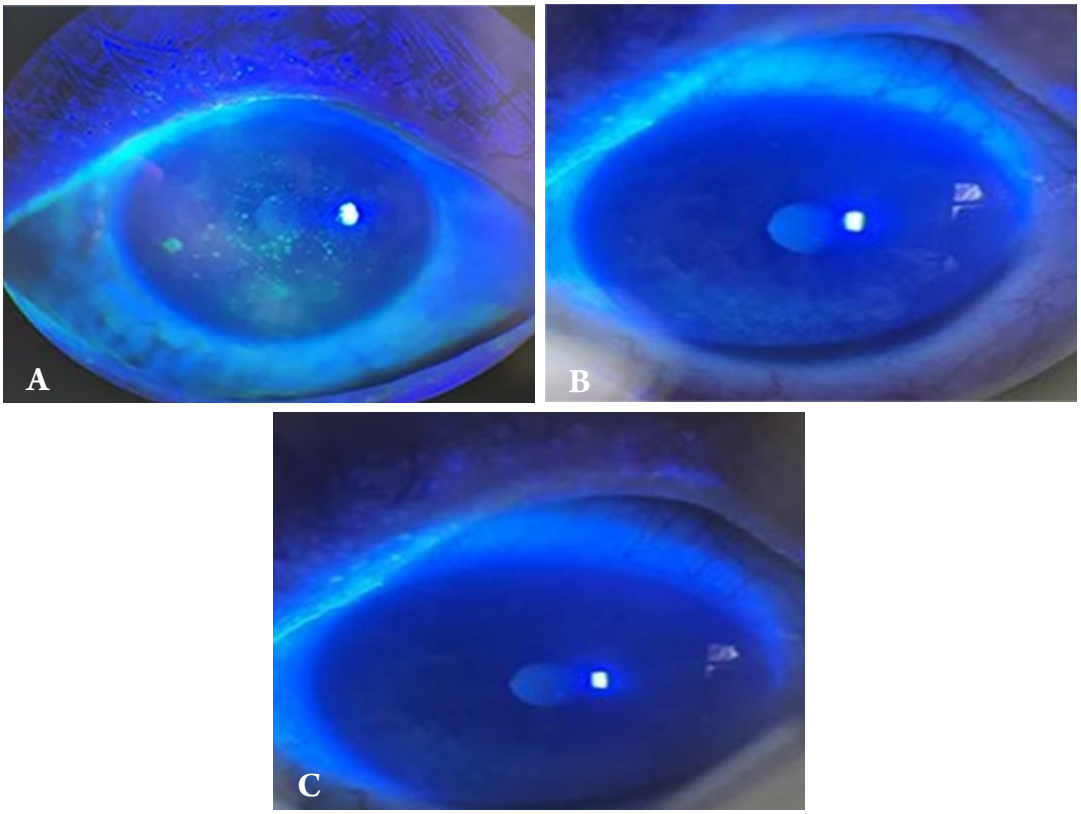

Figure 1. A representative case from group 1. (A) Topical fluorescein-stained right eye with dry eye disease and resistant corneal epithelial defects for 1 month. (B, C) Complete healing after administration of eye drops from cord blood platelet lysate for 1 week.

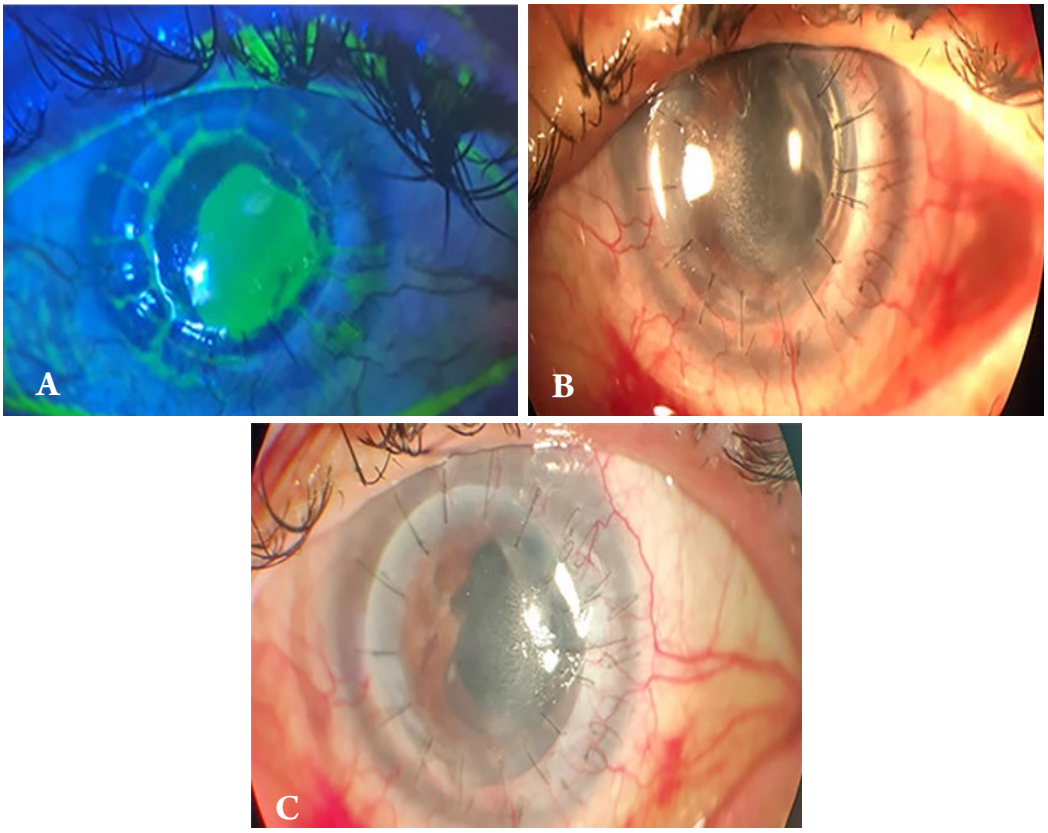

Figure 2. A representative case from group 2. (A) Topical fluorescein-stained eye with resistant corneal ulceration after keratoplasty. (B) Obvious reduction in the epithelial defect size after 1 week and (C) complete healing 2 weeks after administration of eye drops from cord blood platelet lysate.

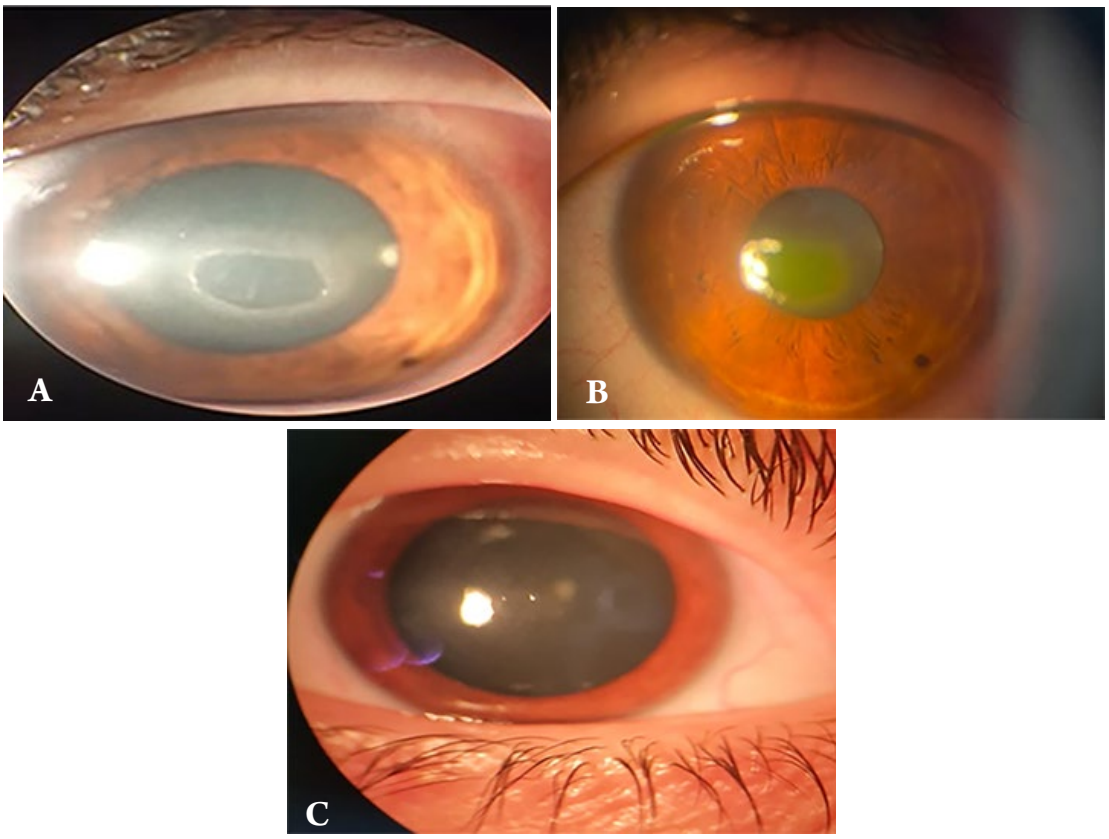

Figure 3. A representative case from group 3. (A) Resistant corneal ulcer following corneal chemical burn. (B) Clear reduction in the epithelial defect size after 2 days and (C) complete healing 1 week after administration of eye drops from cord blood platelet lysate.

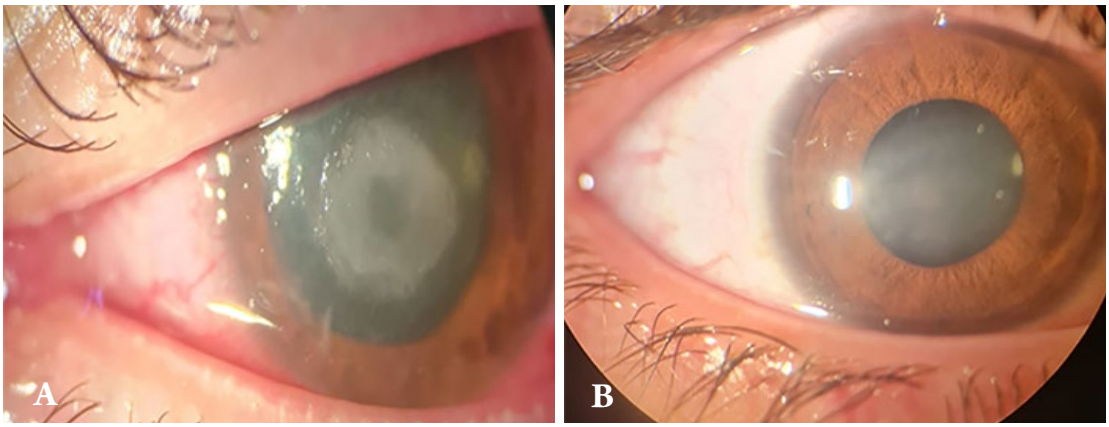

Figure 4. A representative case from group 4. (A) Resistant corneal ulcer after medical treatment of fungal keratitis that is now in a clinically quiescent state. (B) Complete healing 2 weeks after the administration of eye drops from cord blood platelet lysate.

Reprehensive cases

Case 1:

A 70-year-old woman with Sjögren syndrome presented with bilateral severe tear-deficiency dry eye with resistant punctate corneal erosions in the right eye (Figure 1A), complaining of severe photophobia and blurring of vision, with complete healing after 1 week of administration of eye drops from CBPL (Figure 1B, C).

Case 2:
A 60-year-old man presented with a resistant ulcer on a donor corneal graft (Figure 2A) 1 month after uneventful penetrating keratoplasty, with corneal vascularization, and early signs of graft rejection. The eye showed complete healing after 2 weeks of administration of eye drops from CBPL (Figure 2B, C).

Case 3:
A 23-year-old woman presented with a resistant central corneal ulcer (Figure 3A) following corneal alkali chemical burn, with complete healing after 1 week of administration of eye drops from CBPL (Figure 3B, C).

Case 4:
A 36-year-old woman presented with a resistant corneal epithelial defect post-fungal keratitis due to a plant-origin trauma. After intensive therapy with topical antifungal eye drops (voriconazole 1% prepared by a pharmacy unit [Vfend®, Pfizer, Inc., NY, USA]) and a sterile corneal surface, the patient developed a persistent photophobic resistant corneal ulcer (Figure 4A) 1 month later, with complete healing after 2 weeks of administration of eye drops from CBPL (Figure 4B).

DISCUSSION

In this prospective interventional case series, eye drops from CBPL were an effective and safe treatment option for persistent corneal ulcers of different causes.

Platelet activation results in the production of bioactive molecules that play an essential role in tissue regeneration, anti-inflammation, and activation of growth-related signaling pathways that promote healing. Therefore, products containing human platelet lysate have been developed as an alternate treatment for numerous ocular surface conditions, including corneal ulcers and dry eye [25]. Autologous blood has been used in various ocular conditions [26]. Adult peripheral blood contains a greater concentration of inflammatory markers than CB plasma, thereby aggravating corneal ulcer conditions [27]. CB plasma contains chemicals not present in peripheral blood that play a crucial role in immune suppression [28]. This characteristic promotes the preferred use of CB in disorders characterized by aberrant inflammation and autoimmune ocular surface disorders commonly associated with corneal ulcers. CB-PRP has been investigated as a treatment option for different ocular conditions, but the role of CBPL in managing resistant corneal ulcers has rarely been explored. Table 2 summarizes the outcomes of studies that used UC-derived therapeutic materials for various ocular surface and corneal epithelial entities from 2003 to 2022 [24, 29–50].

In the present study, corneal ulcers showed complete healing in 71% of eyes with dry eye, with a mean (SD) duration of 9.5 (3.2) days and a significant improvement in BCDVA at the final follow-up. These results were consistent with Samarkanova et al.'s study [21] involving 46 eyes of 33 patients with PED unresponsive to standard therapies. The patients were administered with allogenic eye drops from CBPL. Improvement was reported for 8 (100%) eyes with severe dry eye.

Garcia-Conca et al. [51] performed a randomized controlled trial (RCT) involving patients with hyposecretory dry eye disease, including 44 eyes administered with eye drops from PRP for 30 days and 39 eyes administered with artificial tears (ATs). The Ocular Surface Disease Index (OSDI) improved with both treatments, although the PRP group showed a greater and more rapid alleviation of symptoms throughout the treatment course. The authors hypothesized that this could be related to time-related deterioration in the biological stability of growth factors and platelets [51]. As we introduced CBPL, these growth factors were immediately and directly in contact with the cornea, which may account for the shortened healing period observed in the present study. However, further studies should verify this finding.

Giannaccare et al. [52] in their RCT enrolled 30 patients with severe dry eye and administered them with eye drops from allogeneic peripheral blood serum (allo-PBS) or CB serum eight times daily for 30 days. The increase in the corneal nerve fractal dimension value from the first to the second visit was higher in CB serum-treated eyes than in allo-PBS-treated eyes [52]. In the present study, the patients with aqueous tear deficiency dry eye and resistant corneal ulcers showed complete healing or improvement with no treatment failure after < 2 weeks of administration of eye drops from CBPL.

Among post-keratoplasty eyes with resistant corneal ulcers, 67% and 33% showed complete healing and improvement, respectively, with a significant improvement in BCDVA in approximately 2 weeks. Similarly, Kamble et al. [29] performed an RCT involving eyes with post-penetrating keratoplasty or post-anterior

Table 2. Summary of the effects of the umbilical cord-derived therapeutic material on the corneal epithelium according to original articles published from 2003 to 2022

First Author (Year of Publishing)	Type of Study	Participants	Outcomes and advantages
Vajpayee et al. (2003) [32]	A prospective randomized controlled clinical trial.	Sixty eyes of 59 patients were divided into the UCS (n = 31) and AS (control; n = 29) groups.	1. The median percentage decrease in the size of ED was significantly greater that in the case group at all follow-ups. 2. A greater number of patients showed complete re-epithelialization with UCS than with AS. 3. Compared to AS, UCS led to faster healing of PED refractory to all medical management.
Yoon et al.(2005) [33]	A prospective interventional study.	Fourteen eyes of 14 patients with PED persistent for at least 2 weeks despite CMT were treated with 20% UCS eye drops six times / day.	1. UCS therapy was effective in six (42.9%) eyes, partially effective in six (42.9%) eyes, and ineffective in two (14.2%) eyes. In eyes in which UCS therapy was ineffective, PED eventually healed within 8 weeks. 2. UCS eye drops effectively treated PED.
Yoon et al. (2006) [34]	A prospective interventional study.	Fifty-five eyes of 31 patients with severe DES were treated with UCS eye drops.	1. Two months after the treatment, the mean symptom score, TBUT, and keratoepitheliopathy score showed significant improvement. 2. UCS contains essential tear components, and UUS eye drops effectively and safely treated severe DES.
Yoon et al.(2007) [35]	A prospective cohort study.	Twenty-four eyes of 12 patients with severe DES associated with GVHD were treated with 20% UCS eye drops.	No significant complications were associated with the use of the eye drops. UCS eye drops safely and effectively treated severe DES associated with GVHD.
Yoon et l. (2007) [31]	A prospective non-comparative case series.	Twenty-eight eyes of 28 patients with neurotrophic keratitis refractory to CMT were recruited.	1. ED healed completely in all eyes, with a mean (SD) healing time of 4.4 (4.0) weeks. After treatment, VA improved by over two lines in 17 (60.7%) eyes. 2. UCS eye drops might effectively manage neurotrophic keratitis.
Yoon et l. (2007) [36]	A case-control study.	Ninety-two eyes of 48 patients with severe DES (34 eyes of 17 patients with Sjogren syndrome and 58 eyes of 31 patients with non-Sjogren syndrome) were treated with 20% AS (41 eyes of 21 patients) or UCS (51 eyes of 27 patients) eye drops.	1. Symptom and keratoepitheliopathy scores were lower at 1 and 2 months for patients treated with UCS than for those treated with AS. 2. In patients with Sjogren syndrome, the goblet cell density was higher after 2 months of UCS treatment than that after 2 months of AS treatment.
Sharma et al.(2011) [30]	A double-blind prospective randomized controlled clinical trial.	Thirty-three eyes of 32 patients with acute ocular chemical burns of grades III – V were randomized into three groups: UCS (n = 12), AS (n = 11), and AT (0.5% HPMC + 0.3% glycerin; n = 10).	1. The mean (SD) time to complete epithelialization was 21.16 (26.81), 56.6 (35.5), and 40.13 (35.79) days in the UCS, AS, and AT groups, respectively, showing significant differences. By day 21, the mean (SD) percentage decrease in the ED diameter was 94.63 (11.99) with UCS, 53.17 (34.81) with AS, and 64.22 (42.43) with AT. 2. UCS therapy was more effective than AS or AT in ocular surface restoration after acute chemical injuries.
Yoon et al. (2011) [37]	A prospective case series study.	Thirty-five eyes of 35 patients with recurrent corneal erosions were studied, 18 of which were treated with 20% UCS eye drops in addition to AT (group A), while 17 were treated with AT alone (group B). The frequency of recurrence of corneal erosions was compared between the two groups.	UCS eye drops may be effective in reducing the number of recurrences in managing recurrent corneal erosions.
Yoon et al. (2013) [38]	A prospective study.	Sixty patients (120 eyes) with myopia who underwent LASEK were included, 32 (64 eyes) of whom were treated with 20% UCS eye drops in combination with CMT (group A), while 28 (56 eyes) were treated with CMT alone (group B).	1. VA or refraction did not differ significantly between groups with a comparable mean time to epithelial healing. The mean (SD) haze scores at 2 and 4 weeks were 0.59 (0.80) and 0.31 (0.54) in group A, respectively, and 1.06 (0.91) and 0.69 (0.78) in group B, respectively, showing a significant difference. 2. Application of 20% UCS eye drops in addition to CMT after LASEK reduced early postoperative corneal haze and improved tear film and ocular surface parameters.

Continued Table 2. Summary of the effects of the umbilical cord-derived therapeutic material on the corneal epithelium according to original articles published from 2003 to 2022

Oh et al. (2012) [39]	Animal and Experimental research study.	UCS eye drops were administrated for corneal wound healing and haze in a mouse model of ocular chemical burn and compared to that of PBS eye drops or AT.	1. The UCS group showed significantly decreased ED parameters compared to the PBS group on days 1 and 2 and compared to the AT group on days 1 – 5. The haze scores were significantly lower in the UCS group than in the PBS group on days 2 and 3 and in the AT group on days 2 – 7. 2. Histological examination showed better epithelial integrity and lower stromal inflammation and edema in the UCS group than in the other groups. 3. UCS eye drops were more effective in improving corneal wound healing and reducing corneal haze than PBS eye drops and AT in this experimental model of chemical burns.
Erdem et al. (2014) [24]	A prospective study.	Sixteen eyes of 14 patients with PED resistant to CMT were treated with 20% UCS eye drops.	1. CBS eye drops were effective in managing PED. The disease grade affected the healing time. 2. The use of CBS eye drops was safe and effective in early-grade PED. 3. Early-onset therapy for at least 3 weeks was necessary for favorable results.
Sharma et al. (2015) [40]	A retrospective, interventional, comparative case series.	Fifty-five eyes with chemical burns of grades III – V who presented within 3 weeks of injury were evaluated. Patients were treated with CMT (20 eyes) alone or combined with UCS (17 eyes) or AMT (18 eyes).	1. UCS and AMT groups showed early epithelialization compared to the CMT group. The mean (SD) time for healing of ED was 57.7 (29.3), 27.4 (19.0), and 41.1 (28.9) days in the CMT, UCS, and AMT groups, respectively. 2. UCS therapy could be a better alternative to AMT in acute moderate to severe ocular chemical burns, as it avoids surgical intervention in inflamed eyes.
Sharma et al. (2016) [41]	A randomized controlled clinical trial.	Forty-five eyes with acute chemical burns of grades III – V presenting within 1 week of injury were randomized into three groups (15 eyes in each group).	1. UCS and AMT, as an adjuvant to CMT in acute chemical injury, were equally effective. 2. UCS has the advantage of faster improvement in corneal clarity, better pain control, and avoidance of surgery in an inflamed eye.
Kamble (2017) [29]	A prospective randomized controlled clinical trial.	A total of 105 eyes with ED after keratoplasty (67 eyes post-penetrating keratoplasty and 38 eyes post-anterior lamellar keratoplasty) on postoperative day 1 were included in the study. The eyes were randomized into three groups: UCS (n = 35), AS (n = 35), and AT (n = 35).	1. Most cases of post-keratoplasty corneal ED can be managed with AT alone. 2. Serum therapy (AS / UCS) helps in faster re-epithelialization of post-keratoplasty ED compared to AT and may be considered as a treatment option for early epithelial healing.
Bakhtyar et al. (2017) [42]	Animal and experimental research study.	Murine corneal abrasion model	UCB provides approximately sufficient acellular gelatinous Wharton's jelly to cover a 115-cm^2 area of wound, it is easy to isolate and available globally. It is a good treatment option when affordable and available wound healing remedies are critically necessary.
Tighe et al (2017) [43]	Animal and experimental research study.	A 2-mm-diameter central corneal epithelial wound in one eye of 48 healthy mice was treated with 10 µL of saline with (n = 24) or without (n = 24) AMUC three times a day for 6 days. The corneal ED was measured using 0.1% fluorescein, while corneal epithelial regularity was measured by assessing light reflected from the corneal surface. Hematoxylin and eosin staining and immunohistochemistry were performed. Safety and toxicity were also assessed by monitoring physical activity and body weight.	Topical AMUC eye drops effectively promoted corneal epithelialization and smoothness. They caused no adverse events, as evidenced by no significant changes in body weight or physical activity of the animals.
Han et al.(2019) [44]	Animal and experimental research study.	The right eyes of mice were injured with NaOH. After alkali injury, one of the following agents was topically administered for 7 days: hAM suspension, hUCS, hPBS, or saline.	All treatments reduced inflammatory reactions and development of corneal opacity. Corneal re-epithelialization was faster in the hUCS group.
Ngan et al. (2019) [45]	A prospective interventional case series.	Thirty-four eyes with PED were treated and followed-up for at least 36 months.	1. Thirty-four (95%) eyes were healed with cell transplantation, 22 of which healed within 1 week postoperatively. 2. Tissue-cultured human CLEC transplantation safely and effectively treated PED.

Continued Table 2. Summary of the effects of the umbilical cord-derived therapeutic material on the corneal epithelium according to original articles published from 2003 to 2022

Azmi et al. (2020) [46]	An *in vitro* study.	hUC-derived MSCs downregulated the expressions of HLA classes I and II in IFN-γ-stimulated human telomerase-immortalized corneal epithelial cells.	1. A new perspective was obtained on the role of hUC-MSC in promoting the growth and functions of human corneal epithelial cells *in vitro*. 2. hUC-MSC promoted corneal epithelial growth and functions.
Moradian et al. (2020) [47]	A double-masked, prospective randomized controlled clinical trial.	Eighty eyes of 80 patients who were candidates for vitrectomy because of proliferative diabetic retinopathy complications were recruited.	UCS significantly accelerated the rate of improvement of PEDs after diabetic vitrectomy and reduced the risk of PED.
Kacham et al.(2021) [48]	An *in vitro* study.	Three samples were obtained from women aged 22 – 27 years with no history of systemic diseases, such as diabetes, cancer, or other metabolic disorders to select the umbilical cord of their neonates.	Umbilical cord-derived MSCs promoted repair of the injured corneal epithelium by stimulating the proliferation of corneal epithelial cells *in vitro*.
Rodriguez Calvo-de-Mora et al.(2022) [49]	A double-blind randomized clinical trial.	Sixty-three patients with severe DES were included, with 21 in each group (AS, allogeneic serum, and UCS). VA, Schirmer's test, TBUT, lissamine green, fluorescein staining measurement, and a questionnaire survey was performed pre-treatment and at the 1- and 3-month follow-ups.	Three treatment arms of the trial were effective in managing severe DES.
Liu et al.(2022) [50]	An *in vitro* and *in vivo* study.	*In vitro* investigation of the mechanism of HUMSC-sEV involvement in corneal epithelial wound healing was performed.	sEVs derived from HUMSCs significantly promoted *in vitro* corneal epithelial cell proliferation, migration, and *in vivo* corneal epithelial wound healing.

Abbreviations: UCS, umbilical cord serum; n, number; AS, autologous blood serum; ED, epithelial defect; PED, persistent epithelial defects; CMT, conventional medical treatment; DES, dry eye syndrome; TBUT, tear break up time; GVHD, graft-versus-host disease; SD, standard deviation; VA, visual acuity; AT, artificial tears; HPMC, hydroxypropylmethylcellulose; LASEK, laser-assisted subepithelial keratomileusis; PBS, peripheral blood serum; CBS, cord blood serum; AMT, amniotic membrane transplantation; CM^2, square centimeters; µL, microliter; AMUC, amniotic membrane, and umbilical cord; NaOH, sodium hydroxide; hAM, human amniotic membrane; hUCS, human umbilical cord serum; hPBS, human peripheral blood serum; CLECs, cord lining epithelial cells; huc, human umbilical cord; MSC, mesenchymal stem cells; HLA, human leukocyte antigen; IFN-γ, interferon-gamma; HUMSC-sEVs, human umbilical cord MSC-derived small extracellular vesicles.

lamellar keratoplasty. A total of 105 eyes with ED after keratoplasty (67 eyes post-penetrating keratoplasty and 38 eyes post-anterior lamellar keratoplasty) on postoperative day 1 were included in their study. The eyes were randomized into three groups: umbilical cord serum (UCS) (n = 35), autologous blood serum (AS) (n = 35), and artificial tears (AT) (n = 35). Most cases of post-keratoplasty corneal ED managed with AT alone. Serum therapy (AS / UCS) helps in faster re-epithelialization of post-keratoplasty ED compared to AT. They recommended serum therapy as an alternative for early management of epithelial repair. The mean (SD) duration of re-epithelialization was 4.46 (61.36) days in the AT-treated eyes, 3.09 (2.17) days in the AS-treated eyes, and 2.54 (62.10) days in the UCS-treated eyes [29].

Samarkanova et al. [21] reported recovery in six (80%) eyes with corneal chemical burns and treatment failure in one (20%) eye. Eyes with corneal chemical burns and resistant corneal ulcers in the present study showed complete healing in 50% of cases and improvement in 50% of cases, with no treatment failure and a significant improvement in BCDVA at the final follow-up. The mean (SD) duration of complete healing was 14.5 (0.7) days. In an RCT for acute ocular chemical burns of different grades conducted by Sharma et al. [30], 33 eyes of 32 patients with acute ocular chemical burns of grades III – V were randomized into three groups: UCS (n = 12), AS (n = 11), and AT (n = 10). The mean (SD) time to complete epithelialization was 21.16 (26.81), 56.6 (35.5), and 40.13 (35.79) days in the UCS, AS, and AT groups, respectively, showing significant differences. By day 21, the mean (SD) percentage decrease in the ED diameter was 94.63 (11.99) with UCS, 53.17 (34.81) with AS, and 64.22 (42.43) with AT. UCS was more effective than AS, because it promoted quicker healing of the epithelial defect with more corneal clarity and less vascularization and limbal involvement [30]. The shorter healing time in the present study may have resulted from the administration of CBPL, which contains higher levels of anti-inflammatory molecules.

Platelet-rich growth factors (PRGF) were compared to ATs in 10 eyes with PED due to grade III – V acute chemical burn by Panda et al. [53]. On day 7, eyes treated with PRGF showed a significantly decreased epithelial defect area, despite no significant difference between the two groups in the total healing time. In addition to the increased corneal transparency and BCDVA, PRGF-treated eyes showed enhanced corneal transparency [53]. Similarly, all study groups showed significantly improved BCDVA. Moreover, eyes with chemical burn experienced complete healing or improvement with an approximately 2-week administration of eye drops from CBPL.

Group 4 showed complete healing in 63% of eyes, improvement in 12% of eyes, and treatment failure in 25% of eyes (two eyes with limbal stem cell deficiency and two eyes with neurotrophic keratitis). The mean (SD) duration of complete healing was 11.7 (4.1) days with a significant improvement BCDVA at the final follow-up. Similarly, Samarkanova et al. [21] reported improvement in 12 (85%) patients with chronic corneal conditions, and worsening in both eyes despite treatment in one (15%) patient.

Sanchez-Avila et al. [54], evaluated 38 eyes with stages 2 – 3 of neurotrophic keratitis treated with eye drops from PRGF. Most (97.4%) patients had full resolution of corneal epithelial defects or ulcers. The mean (SD) resolution period lasted 11.4 (13.7) weeks. Observations revealed a significant reduction in the OSDI score (60.9%) and improvement in BCDVA (52.8%) [54]. Yoon et al. [31], evaluated 28 eyes of 28 patients with neurotrophic keratitis refractory to conventional medical treatment. PED healed completely in all eyes, with a mean (SD) healing time of 4.4 (4.0) weeks. After treatment, visual acuity improved by over two lines in 17 (60.7%) eyes. They found UCS to be an effective treatment of severe dry eye conditions accompanied by neurotrophic keratitis. However, in the present study, treatment failure occurred in eyes with neurotrophic keratitis (two eyes in group 4) despite administration of eye drops from CBPL for approximately 2 weeks.

Kim et al. [55] treated a total of 28 eyes with PED after infectious keratitis and found that the corneal epithelium repair rate was considerably greater in the PRGF group than in the AS group. In a study by Lopez-Plandoli et al. [56], PRGF triggered by calcium was utilized to treat 18 patients with PED, 85% of whom exhibited remission after 11 weeks. CBPL is abundant in growth factors, stem cells, and immunosuppressive properties and lack cytokines, which are the drawbacks of AS. Furthermore, it can be a viable long-term storage option for public CB banks [21]. As the duration of PED is usually proportional to the period required for its healing and likelihood of PED-related problems [57-59], the benefit of rapid healing provided by eye drops from CB from platelet lysate is crucial. Thus, UCB derivatives can be utilized to decrease the time of recovery when availability is not an issue. The overall healing time was approximately less than 2 weeks in the present study after regular administrations of eye drops from CBPL with no attributable adverse effects. Out of 40 eyes with persistent corneal ulcer, 26 (65%), 10 (25%), and four (10%) eyes showed complete healing, improvement, and treatment failure, respectively, with a significant improvement in the final BCDVA in all groups.

The strength of the present study was the use of CBPL in cases of persistent corneal ulcer with different causes. It was an effective and safe treatment modality for corneal healing. However, large-scale, multicenter prospective clinical trials are required to validate the present findings with a longer follow-up and the use of CBPL in other corneal disorders. Further studies are required to evaluate the long-term safety of this therapy in human ophthalmic disorders, clarify pharmacokinetic aspects, and provide a standardized therapeutic scheme for the clinical use of UCB. Other limitations are the small number of patients examined for each entity, varying severity of clinical symptoms on presentation, and absence of contemporaneous controls treated with conventional treatment. Moreover, clinical variables, such as corneal inflammation, conjunctivalization, corneal neovascularization, or pain, were not assessed individually. Future randomized clinical trials with a large sample size and a long follow-up are required to address these limitations and confirm our preliminary outcomes.

CONCLUSIONS

Eye drops from CBPL significantly improved BCDVA post-treatment with complete healing in most cases with persistent corneal ulcer of differet causes. The findings of the present study suggested that eye drops from UBPL could be an effective and safe treatment option for persistent corneal ulcers of different causes. Future randomized clinical trials with a large sample size and a long follow-up are required to confirm these preliminary outcomes.

ETHICAL DECLARATIONS

Ethical approval: The Institutional Review Board of Mansoura University, Faculty of Medicine, Mansoura, Egypt, approved the study protocol (approval code number: R.21.05.1338). All study procedures were performed in accordance with the tenets of the Declaration of Helsinki by the World Medical Association. All patients provided written informed consent. CB units were collected at the Obstetric Unit of the Mansoura University Hospital. Prenatally, the mothers filled out a donor consent form authorizing the use of these samples for research and validation.

Conflict of interest: None.

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