·Clinical Research·

Umbilical cord blood serum therapy for the management of persistent corneal epithelial defects

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Abstract

• AIM: To evaluate the role of umbilical cord blood serum (CBS) therapy in cases with persistent corneal epithelial defects (PED).

• METHODS: Sixteen eyes of 14 patients with PED who were resistant to conventional treatment were treated with 20% umbilical cord serum eye drops. Patients were followed –up weekly until epithelization was complete. The collected data included the grade of corneal lesion (Grade I: epithelial defect +superficial vascularization, Grade II: epithelial defect +stromal edema, Grade III: corneal ulcer +stromal melting), the size of epithelial defect (pretreatment, 7th, 14th and 21st days of treatment), and follow-up time was evaluated retrospectively.

• RESULTS: The mean size of epithelial defect on two perpendicular axes was 5.2×4.6-mm² (range: 2.5-8 mm× 2.2 -9 mm²). Mean duration of treatment was 8.3 ±5wk. CBS therapy was effective in 12 eyes (75%) and ineffective in 4 eyes (25%). The epithelial defects in 4 ineffective eyes were healed with amniotic membrane transplantation and tarsorrhaphy. The rate of complete healing was 12.5% by 7d, 25% by 14d, and 75% by 21d. The healing time was prolonged in Grade III eyes in comparison to eyes in Grade I or Grade II.

• CONCLUSION: The results of the current study indicated the safety effectiveness of CBS drops in the management of PED. The grade of disease seems have a role on the healing time.

• KEYWORDS: persistent corneal epithelial defect; umbilical cord serum eye drop; neurotrophic keratitis

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INTRODUCTION

Persistent corneal epithelial defects (PED) are one of the challenging problems in ophthalmology practice. It may develop result of various conditions; such as chemical burns, neurogenic, infectious and immunological disorders, trauma, corneal epithelial and basement membrane disorders[1,2].

Conventional treatments for PED includes artificial tear drops, therapeutic contact lenses, amniotic membrane transplantation and tarsoraphy. Sometimes these options may fail to manage this condition and patients need the substances that enhance epithelial differentiation and proliferation.

Some studies showed that autologous serum contains many substances like vitamin A, transforming growth factor-A , fibronectin, and helps to recover PED [3-5]. The main limitation of autologous serum therapy is the need of repeated blood collection from patients. Umbilical cord blood serum (CBS) contains many growth factors in higher concentration and also leads to fasten healing of PED comparison to autologous seru[6-8]. Beside of many conducted studies on this issue, that is not clear yet the efficiency of CBS treatment in PED patients with different clinical severity. In the present study, we investigated the efficacy of umbilical cord serum eyedrops for the treatment of patients with PED in respect of a severity grading system.

SUBJECTS AND METHODS

Sixteen eyes of 14 patients with persistent epithelial defect were included to the study group. Persistent corneal epithelial defect was defined as a corneal defect with a minimum diameter of 2 mm along the greatest axis persisting for at least 2wk without improvement despite conventional treatments[8].

Patients with active lid or ocular infections, severe limbal ischaemia, inflammatory corneal disorders such as Mooren's ulcer and rheumatoid arthritis, pregnant and lactating women

were excluded from the study.

Institutional ethic committee approval was obtained from the Cukurova University Faculty of Medicine and the study protocol followed the guidelines of Helsinki Declaration.

Patients underwent complete ophthalmic examination which involved best corrected visual acuity and slit-lamp biomicroscopy on each visit. The patients were examined daily at first week, thereafter weekly until completion of epithelization. Slit-lamp photographs were taken at each visit and were evaluated retrospectively. The size of the epithelial defect was measured at its largest dimension on two perpendicular axes with the micrometer of slit-lamp. The grading system, which was developed for neurotrophic keratitis, was used for defining the clinical features of the lesions [9]. The healing was defined as completion of epithelization with relief of symptoms. The changes of lesion size were recorded at the 7th, 14th and 21st days of treatment. According to this system, grade 1 eyes were characterized by epithelial defect, superficial vascularization and stromal scarring; grade 2 eyes, by epithelial defect with stromal edema; and grade 3 eyes; by ulceration and stromal melting.

The cord blood serum eyedrops were prepared using a previously reported method by Yoon *et al* [6]. Umbilical cord blood was obtained from mothers who underwent vaginal or cesarean section delivery. Laboratory data for hepatitis B and C virus and human immunodeficiency virus (HIV) were examined two times (at 8 and 38 gestational weeks). After fetal delivery, a volume of 100 mL of the umbilical cord blood was collected from the umbilical vein. Obtained umbilical cord blood was clotted for 30min at room temperature. After centrifugation at 1500 rpm for 5min, serum was isolated and diluted to 20% concentration with unpreserved saline solution. Patients were instructed to keep the bottle at -4℃ in a refrigerator. The maximum storage time in freezer was 3mo. Patients were also instructed to instill umbilical cord serum eyedrops 10 times a day in addition to topical antibiotic drop 5 times daily (lomefloxacin). Preservative-free artificial tears were instilled 4 times a day simultaneously with the umbilical cord serum at 10-minute intervals. After two week, umbilical cord serum eyedrops were instilled continuously 5 times a day. At the 21st day of treatment amniotic membrane transplantations was performed to the patients whose lesions did not heal with topical therapy.

RESULTS

Among 14 patients (16 eyes) with persistent corneal epithelial defect, 10 patients were male and 4 were female. The mean age was 45.9y (range, 12-77y).

Causes of persistent corneal epithelial defect was neurotrophic keratitis in 6 patients (herpes zoster ophthalmicus in 3, diabetes in 2, trigeminal neuralgia in 1), bullous keratopathy in 2 patients, exposure keratopathy in 3 patients, alkaline burn in 3 patients and topical anesthetic drop (proparacaine hydrochloride 0.5% ophthalmic solution) abuse related keratopathy in 2 patients.

The mean duration of persistent corneal epithelial defect prior to umbilical cord serum therapy was 31.5±12.4d (range, 18-43d). The mean size of epithelial defect on two perpendicular axes was 5.2×4.6-mm^2 (range: 2.5-8 mm×2.2-9 mm). According to the grading system, 2 eyes (12.5%) had grade 1 disease, 10 eyes (62.5%) had grade 2 and 4 eyes (25%) had grade 3 disease. The demographic and clinical features of patients are summarized in Table 1.

Umbilical cord serum drop was applied for at least 3wk in all patients. The mean time of treatment was 59.3±33.5d (range, 21-102d) and the mean healing time was 22.5±15.4d (range, 4-54d; Figure 1). There was no recurrence during the follow-up period. The rate of complete healing was 12.5 % by 7d, 25% by 14d, and 75% by 21d. None of grade 3 eyes healed at the end of 3rd wk, other surgical procedures (amniotic membrane transplantation, tarsorrhaphy) were performed in addition to umbilical cord serum theraphy for these eyes. There was no light perception in two eyes at the beginning, otherwise mean pre-and post-treatment visual acuities was 0.1±0.016 and 0.3±0.06 respectively in other 14 eyes. Visual acuity did not get worse in these 14 eyes.

DISCUSSION

PED may lead to severe ocular morbidity and the main goal of therapy includes elimination of any cause and restoration of ocular surface. Surgical treatment may be necessary in some situations, such as lid surgery for entropium or punctal plug insertion for dry eye. In fact, ocular surface restoration is an end point of successful PED therapy.

The essential tear components have a significant role on the proliferation, differentiation, and maturation of human corneal epithelium. Some of these are epithelial growth factor (EGF) , vitamin A, tumor growth factor-b (TGF-b), fibroblast growth factor and fibronectin[4,10,11]. Several studies has shown that autologous serum and CBS includes many of these tear components [3-6]. The epitheliotropic features of CBS in promoting limbal stem cell activity has been demonstrated in an *ex vivo* cell culture model [12]. CBS also shown the highest ability to promote epithelial proliferation and differentiation when compared with peripheral blood serum and fresh frozen plasma[13].

More recently, a novel treatment has been proposed for the treatment of PED, consisting of plasma rich in growth factors[14]. CBS therapy has many advantages over autologous serum therapy. One of these is, a large amount of blood can be drawn from umbilical vein, so it can be prepared for several patients at the same time [15,16]. CBS contains some special growth factors such as TGF-b, EGF which are three times higher than those in autologous serum[6].

Recent studies reported the efficiency of umbilical cord

Table 1 Demographics, clinical features and corneal lesion changes of patients with umblical cord serum therapy

Patient No.	Age	Gender	Eye	Primary diagnosis	Grade	Epithelial defect size (mm^2)	Healing rate (%) of lesion at			Healing time (d)	Additional procedures
							7^{th} d	14^{th} d	21^{th} d		
1	70	F	R	Bullous keratopathy	3	9.2×8	0	5	10	51	Amniotic membrane transplantation
2	74	F	R	Exposure keratopathy	1	3.4×2.5	0	50	100	21	-
3	12	M	L	Alkaline burn	2	11×11	50	85	100	21	-
4	70	M	R	Bullous keratopathy	3	4.7×5	5	15	25	45	Amniotic membrane transplantation
5	14	F	L	Neurotrophic keratopathy	2	6.1×5.5	50	95	100	18	-
6	17	F	R	Neurotrophic keratopathy	2	2.5×2.4	95	100	100	10	-
			L	Neurotrophic keratopathy	2	5.1×4.6	75	80	100	20	-
7	41	M	L	Exposure keratopathy	2	7.2×3.9	25	65	100	18	-
8	21	M	L	Neurotrophic keratopathy	2	8.1×7.5	75	85	100	16	-
9	70	M	R	Exposure keratopathy	3	6.1×3.5	65	75	65	32	Tarsorrhaphy
10	58	M	R	Alkaline burn	3	5.4×8	85	85	80	54	Amniotic membrane transplantation
11	68	M	R	Neurotrophic keratopathy	2	5.4×2	45	50	100	18	-
12	77	M	R	Neurotrophic keratopathy	2	2.5×2	100	100	100	5	-
13	19	M	R	TAD[1] abuse related keratopathy	2	2×2.4	95	100	100	8	-
			L	TAD[1] abuse related keratopathy	2	2.4×2.1	90	95	100	15	-
14	32	M	R	Alkaline burn	1	2.3×2.1	100	100	100	4	-

TAD[1]: Topical anesthetic drug (proparacaine hydrochloride 0.5%); [2]Longest diameters in two perpendicular axis; R: Right eye; L: Left eye.

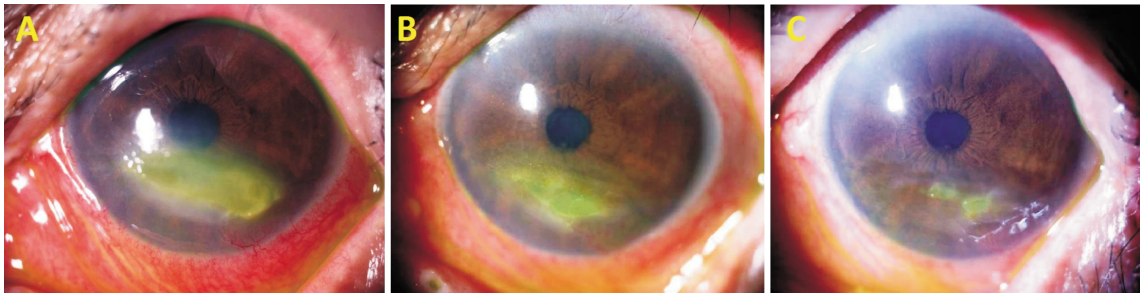

Figure 1 Healing of persistent corneal epithelium defect with umbilical cord serum therapy (Case No. 7) A: Before treatment; B: 1st wk of the treatment; C: 3rd wk of the treatment.

serum eyedrops in the treatment of dry eye, recurrent corneal epithelial erosions, acute ocular chemical burn, and neurotrophic keratitis [6,8,16-19]. The common point of these reports was the assistance of CBS therapy in restoration of damaged ocular surface. Our cases had various ethiological factors for development of PED (neurotrophic, alkaline, exposure, bullous, and TAD abuse keratopathy). The common points for these cases were the efficiency of CBS and the role of PED grade on healing.

Versura *et al* [20] reported that a favorable effect of cord serum drop on ocular discomfort symptoms and tear osmolarity results. They also showed a significant improvement at corneal esthesiometry score with cord serum therapy. Our observations indicated that CBS treatment was not adequate for managament of deep corneal ulcers. Additional surgical options such as amniotic membrane transplantation or tarsoraphy were necessary for high grade PED. CBS treatment seems effective for PED in corneas without stromal bed thinning.

The healing rate of cases with neurotrophic keratitis related

PED has been reported as 28.6% within 2wk and 78.6% within 4wk [7]. The results of current study were similar with previous reports, healing rate was 25% at the end of 2nd wk and 75% 4th wk. We concluded that CBS therapy should be continued at least 3wk for complete healing.

Besides of many favorable features, the risk of allergies and transmitting of parenteral microorganisms should be taken into consideration before starting CBS therapy. In this case series, we did not observe any side effect of CBS treatment within follow-up time.

This study has several limitations, including a small sample size, no control group, and its retrospective study design. One of its strengths is that patients were evaluated in respect to clinical severity of PED which using may help clinicians to decide of treatment duration and efficiency at the presentation.

In conclusion, the use of CBS drops seems to be a safe and effective therapy in cases of early grade PED. The results of this study correlated with previous reported studies. Early onset to therapy and at least three weeks continuing it appears to be necessary for favorable results.

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