Umbilical Cord Serum Eye Drops for Severe ocular surface disease

HEALTH TECHNOLOGY ASSESSMENT SECTION
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DISCLOSURE

The author of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

EXECUTIVE SUMMARY

BACKGROUND

Blood preparations such as autologous serum (AS) are plasma rich in growth factors, platelets, while umbilical cord serum (UCS) contain a high concentration of biologically active components and growth factors. The tear film consists of mucin, aqueous, and lipid layers and contains many growth factors and vitamin A, which are essential for regulating the proliferation, differentiation, and maturation of the ocular surface epithelium. Ocular surface disorders including dry eye disease or keratoconjunctivitis sicca are characterized by a decrease in quality and quantity of the tear film and squamous metaplasia of the conjunctival epithelium. Dry eye syndrome also called *keratoconjunctivitis sicca* is the eye disease in which eyes cannot make enough tears to keep proper eye lubrication and cleansing function. Conventional treatments for ocular surface disorders include the application of artificial tears, topical anti-inflammatory agents, secretagogues, therapeutic contact lenses, and punctal occlusion. Because peripheral blood serum (PBS) harbors essential tear components and growth factors, AS eye drops have been used for the treatment of severe ocular surface diseases. It was found that UCS contains a higher level of essential tear components, growth factors, and neurotrophic factors than AS.

This review was requested by a Consultant Ophthalmologist from Ophthalmology Department, Kuala Lumpur Hospital, Ministry of Health Malaysia (MOH) to assess the effectiveness, safety and cost-effectiveness of using UCS eye drops for the treatment of ocular surface disorders especially for patients that is not effective using AS eye drops.

OBJECTIVE / AIM

The objective of this systematic review was to assess the effectiveness, safety and cost-effectiveness of using UCS eye drops for the treatment of ocular surface disorders.

RESULTS AND CONCLUSIONS

A total of 353 titles were identified through the Ovid interface and PubMed. Ten articles related to the treatment of severe ocular surface diseases using UCS eye drops was included in this review consisting of two randomised controlled trial, one non-randomised clinical trial and seven interventional studies. The studies were conducted in Korea, Italy, India and Turkey.

From the above review it was found that there was fair to high level of evidence to show that UCS eye drops may have potential in the treatment of severe ocular surface diseases such as dry eye syndrome, corneal epithelial defect, neurotrophic keratitis, acute ocular chemical burns and after laser epithelial keratomileus. The majority of the studies were of controlled trials and interventional studies. However, most of the studies were limited by the small number of subjects and the short duration of study. Two randomised controlled trials comparing UCS eye drops versus AS drops showed better improvement using the UCS eye drops. From the studies the authors suggested that UCS eye drops were safe. The UCS eye drops manufacturing need to be done by a certified laboratory and personals who can handle the preparation. Issue of consent from patients who agree to donate cord blood, the testing for infectious diseases such as HIV, Hepatitis C, syphilis etc. also need to be addressed.

The estimated cost for 40 x 1ml of segmented UCS eye drops produced by the Cord Blood Bank Division, National Blood Centre is about RM152.20 for one patient (The estimation cost does not include labour cost, equipment charges and maintenance charges).

METHODS

Electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-process and other Non-indexed citations and Ovid MEDLINE® 1948 to present, EBM Reviews - Cochrane Central Register of Controlled Trials – August 2015, EBM Reviews - Cochrane Database of Systematic Reviews - 2009 to August 2015, EBM Reviews - Health Technology Assessment – 2nd Quarter 2015, EBM Reviews - Database of Abstracts of Reviews of Effects – 2nd Quarter 2015, EBM Reviews – NHS Economic Evaluation Database 2nd Quarter 2015, Embase – 1988 to 2015 week 35. Searches were also run in PubMed. Google was used to search for additional web-based materials and information. No limits were applied. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 1st September 2015.

Umbilical Cord Serum Eye Drops for Severe ocular surface disease

1. BACKGROUND

Blood preparations such as autologous serum (AS) are plasma rich in growth factors, platelets, while umbilical cord serum (UCS) contain a high concentration of biologically active components and growth factors. The tear film consists of mucin, aqueous, and lipid layers and contains many growth factors and vitamin A, which are essential for regulating the proliferation, differentiation, and maturation of the ocular surface epithelium.[1] Ocular surface disorders including dry eye disease or keratoconjunctivitis sicca are characterized by a decrease in quality and quantity of the tear film and squamous metaplasia of the conjunctival epithelium.[1-2] Dry eye syndrome also called *keratoconjunctivitis sicca* is the eye disease in which eyes cannot make enough tears to keep the proper eye lubrication and cleansing function. Conventional treatments for ocular surface disorders include the application of artificial tears, topical anti-inflammatory agents, secretagogues, therapeutic contact lenses, and punctal occlusion.[1-3] Because peripheral blood serum (PBS) harbors essential tear components and growth factors, AS eye drops have been used for the treatment of severe ocular surface diseases. It was found that UCS contains a higher level of essential tear components, growth factors, and neurotrophic factors than AS.[4, 5]

This review was requested by a Consultant Ophthalmologist from Ophthalmology Department, Kuala Lumpur Hospital, Ministry of Health Malaysia (MOH) to assess the effectiveness, safety and cost-effectiveness of using UCS eye drops for the treatment of ocular surface disorders especially for patients that is not effective using AS eye drops.

2. OBJECTIVE / AIM

The objective of this systematic review was to assess the effectiveness, safety and cost-effectiveness of using umbilical cord blood serum eye drops for the treatment of ocular surface disorders.

3. TECHNICAL FEATURES

Umbilical cord blood can be obtained from mothers during delivery. From donors, laboratory examination should be performed at eight and 38 gestational weeks to test for human immunodeficiency and hepatitis B and C viruses. After fetal delivery, about 60 to 80 ml of umbilical cord blood is sampled from the umbilical cord vein. The blood is kept for two hours at room temperature. After fifteen minutes of centrifugation at 3,000 ×g, the serum is carefully isolated under sterile conditions. The serum is then diluted to a 20% concentration with balanced salt solution. The aliquots of diluted serum are placed into sterile 5-ml bottles with ultraviolet light protection. Opened bottles are kept in a refrigerator at 4 ^{0}C for seven days, and unopened bottles are stored in a freezer at −20 ^{0}C for three to six months. UCS eye drops are usually instilled four to six times per day as required in addition to artificial tears and antibiotics.[1] Among the components of serum, EGF, vitamin A, and TGF-β are well preserved for up to one month in a refrigerator at 4 ^{0}C and up to three months in a freezer at −20 ^{0}C.[6] A strict protocol for preparation and storage is essential for the safety of serum use. It was claimed that topical administration of UCS eye drops does not cause adverse effects on the eye, because the components of serum include growth factors and tear components, rather than umbilical cord tissue-derived cells, which may result in

reduced immunogenicity.[7] Serum has a bacteriostatic effect because it contains antibacterial agents such as IgG, lysozyme, and complement. In addition, because serum contains no preservatives, serum therapy can avoid the risk of toxic reaction in the ocular surface.

4. METHODS

4.1. Searching

Electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-process and other Non-indexed citations and Ovid MEDLINE® 1948 to present, EBM Reviews - Cochrane Central Register of Controlled Trials – August 2015, EBM Reviews - Cochrane Database of Systematic Reviews - 2009 to August 2015, EBM Reviews - Health Technology Assessment – 2nd Quarter 2015, EBM Reviews - Database of Abstracts of Reviews of Effects – 2nd Quarter 2015, EBM Reviews – NHS Economic Evaluation Database 2nd Quarter 2015, Embase – 1988 to 2015 week 35. Searches were also run in PubMed. Google was used to search for additional web-based materials and information. No limits were applied. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 1st September 2015.

Appendix 1 showed the detailed search strategies.

4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full text articles for final article selection.

The inclusion and exclusion criteria were:

Inclusion criteria

Population	Patients with: Ocular surface disorders including dry eye disease or keratoconjunctivitis sicca Sjögren's syndrome ocular chemical burn
Interventions	Umbilical cord serum eyedrops
Comparators	Conventional treatments such as artificial tears, topical anti-inflammatory agents, secretagogues, therapeutic contact lenses, punctal occlusion, AS eye drops
Outcomes	• Symptom score • Tear film break-up time (BUT) • Keratoepitheliopathy score • Goblet cell density • Impression cytologic findings. • reduction in corneal epithelial • Discomfort symptoms

	• Corneal sensitivity • epithelial defect
Study design	Health Technology Assessment (HTA), Systematic Review, Randomised Controlled Trial (RCT), Non Randomised Controlled Trial, cross sectional studies, case control studies, case series.
	English full text articles

Exclusion criteria

Study design	Studies conducted in animals and narrative reviews
	Non English full text articles

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and graded according to US/Canadian preventive services task force (Appendix 2). Data were extracted and summarised in evidence table as in Appendix 3.

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5. RESULTS AND DISCUSSION

A total of 353 titles were identified through the Ovid interface and PubMed. Ten articles related to the treatment of severe ocular surface diseases using UCS eye drops was included in this review consisting of two randomised controlled trial, one non-randomised clinical trial and seven interventional studies. The studies were conducted in Korea, Italy, India and Turkey.

5.1 Effectiveness

5.1.1 Treatment of Dry eye Syndrome

Yoon KC et al. in 2006 investigated the efficacy of UCS eye drops for the treatment of severe dry eye syndrome at the Chonnam National University Medical School, Gwangju, South Korea by doing a pre and post interventional study. Fifty-five eyes of 31 patients with severe dry eye syndrome who were refractory to conventional treatments and had symptoms of dry eye for more than three months, low tear film break-up time (BUT=G5 seconds), low Schirmer test (5 mm), and positive fluorescein or rose bengal vital staining (Q3) were included. Twenty patients (38 eyes) of them had Sjo¨gren syndrome. Among eleven patients (17 eyes) who did not have Sjo¨gren syndrome, six patients (eight eyes) had chemical burns, three patients (six eyes) had Stevens-Johnson syndrome, one patient (two eyes) had cicatricial pemphigoid, and one patient (one eye) had herpetic keratitis were included. These patients were treated with umbilical cord serum eyedrops. Symptom scoring tear film break-up time (BUT), Schirmer test, corneal sensitivity test, and corneal fluorescein staining were performed before giving umbilical cord serum eye drops, one month and two months after treatment, and conjunctival impression cytology was also performed before and two months after treatment. The concentrations of epidermal growth factor (EGF), vitamin A, and transforming growth factor-A (TGF-A) in UCS and normal peripheral blood serum was measured.[8 level II-3] The results showed that:
Two months after treatment, significant improvement was observed

- In symptom score (from 3.07 ± 0.54 to 0.96 ± 0.58),
- Tear film break-up time (BUT) (from 3.96 ± 1.56 to 5.45 ± 2.54 seconds), and
- Keratoepitheliopathy score (from 4.87 ± 3.22 to 1.71 ± 1.84) (P<0.01).
- There was no statistically significant change in Schirmer and corneal sensitivity tests.
- In impression cytology, the grade of squamous metaplasia (from 2.35 ± 0.72 to 1.44± 0.69)
- Goblet cell density (from 80.91 ± 31.53 to 154.68 ± 43.06 cell/mm^2) improved significantly (P < 0.01).

The mean concentration of EGF was 0.48 ± 0.09, TGF-A was 57.14 ± 18.98, and vitamin A was 230.85 ± 13.39 ng/mL in umbilical cord serum. The mean concentration of EGF was 0.14 ± 0.03, TGF-A was 31.30 ± 12.86, and vitamin A was 372.34±22.32 ng/mL in peripheral blood serum.

From the above study, the authors mentioned that the study showed that UCS eye drops contained essential tear components, and UCS eye drops may be effective and safe for the treatment of severe dry eye syndrome.

Yoon KC et al. in 2007 study did a non-randomised controlled trial at the Chonnam National University Medical School, Gwangju, South Korea, to compare the therapeutic effect between AS and UCS eye drops in the treatment of severe dry eye syndrome. Ninety-two eyes of 48 patients with severe dry eye syndrome (34 eyes of 17 patients with Sjögren syndrome and 58 eyes of 31 patients with non-Sjögren syndrome) were treated with either 20% AS eye drops (41 eyes of 21 patients) or UCS eye drops (51 eyes of 27 patients). Symptom scoring, corneal sensitivity test, BUT, Schirmer test, tear clearance rate (TCR), corneal fluorescein staining, and conjunctival impression cytologic analysis were performed before and one month and two months after treatment. Both AS and UCS eye drops treatments led to improvement in the symptom score, BUT, keratoepitheliopathy score, and impression cytologic findings. Changes of symptoms after AS or UCS eye drops with severe dry eye syndrome were as below: [9] level II-1

- Symptom score was lower at one month from 3.08±0.48 to 0.98 ± 0.55 for those treated with UCS eye drops compared to AS eye drops , from 2.98 ± 0.42 to 1.24± 0.64 (p = 0.03)
- Symptom score was lower at two months from 3.08±0.48 to 0.94 ± 0.558 for those treated with UCS eye drops compared to AS eye drops , from 2.98 ± 0.42 to 1.20± 0.56 (p = 0.04)
- Keratoepitheliopathy was lower at two month from 5.62 ± 3.19 to 1.75 ± 1.90 for those treated with UCS eye drops compared to AS eye drops , from 5.54 ± 2.84 to 2.34 ± 1.73 (p = 0.02)

Changes of symptoms after AS or UCS eye drops with Sjögren syndrome were as below:

- Goblet cell density was higher at two months of UCS treatment from 82.80 ± 29.41 to 150.25 ± 43.06 compared with AS treatment from 84.00 ± 39.33 to 120.93 ± 24.62 (p =0 .04).

Hence from the above study, the authors concluded that UCS eye drops seems to be more effective in decreasing symptoms score and keratoepitheliopathy in severe dry eye syndrome and increasing goblet cell density in Sjögren syndrome compared with AS eye drops.

Versura P et al. did a pre and post intervention study at the University of Bolognia and S. Orsala-Malpighi Hospital, Italy whereby seventeen graft-versus-host disease (GVHD) and thirteen Sjogren syndrome patients with severe persistent corneal defects were enrolled in the framework of a registered clinical trial (ClinicalTrials.gov NCT01234623). Sterile UCS eye drops were prepared to supply 0.15 ng per eye per day epithelial growth factor and administered for one month in a one day dose dispensing. The extent of epithelial defect was evaluated in square millimeters area, and subjective symptom score (Ocular Surface Disease Index score), Schirmer test I, break-up time, tear osmolarity, corneal sthesiometry (Cochet–Bonnet esthesiometer), conjunctival scraping, and imprint cytology with goblet cell count were performed at baseline (V0) and after 15 days (V1) and 30 days (V2, endpoint) of treatment.[10 level II-3] Satisfaction and tolerability questionnaires were evaluated at V1 and V2. Results showed that:

- A significant reduction was shown at the endpoint versus baseline in corneal epithelial damage (mean ± SD, 16.1 ± 13.7 vs. 40.9 ± 30 mm^2/area, respectively),
- Discomfort symptoms (Ocular Surface Disease Index score, 22.3 ± 10.3 versus 39.3 ± 16.9),
- Scraping cytology score (3.8 ± 1.2 versus 6.6 ± 2.1),
- Tear osmolarity (312.5 ± 7 versus 322 ± 9.1 mOsm/L),
- Significant improvement was shown in corneal esthesiometry (48.2 ± 2.1 versus 49.7 ± 2.1 nylon/mm/ length, P <0.05).

The author concluded that UCS eye drops represent a promising therapeutic approach in the healing of severely injured corneal epithelium and in subjective symptom relief.

Yoon KC et al. in 2007 did a pre and post interventional study to investigate the therapeutic effect of UCS eye drops on dry eye associated with graft-versus-host disease (GVHD). Twenty-four eyes of twelve patients with severe dry eye syndrome associated with GVHD were treated with 20% UCS eye drops. Symptom scoring, corneal sensitivity test, BUT, Schirmer test, TCR, and corneal fluorescein staining were performed before and two and six months after treatment.[11 level II-3] Results showed that:

- Six months after treatment, significant improvement was observed in symptom score (from 3.83 ± 0.38 to 0.83 ± 0.57, $p < 0.01$),
- Corneal sensitivity (from 52.08 ± 6.06mm to 57.50± 3.00mm, $p < 0.01$),
- Tear film break up time (BUT) - from 2.50 ± 0.91 s to 5.71 ± 1.04 s, $p <0.01$),
- Keratoepitheliopathy score (from 7.42 ± 2.02 to 1.29 ± 0.46, $p < 0.01$).
- There was no siginificant change in Schirmer test and TCR results.

From the study the authors suggested that UCS eye drops may be an effective way to treat severe dry eye associated with GVHD.

5.1.2 Treatment of Corneal Epithelial Defect

Yoon KC et al. in 2005 did an interventional study to evaluate the therapeutic effect of UCS eye drops in the treatment of persistent epithelial defect of the cornea. Fourteen eyes of 14 patients with persistent epithelial defect that had persisted for at least two weeks despite conventional treatment were treated with 20% UCS eye drops six times a day. The images of the epithelial defects were captured using a camera attached to a slit lamp biomicroscope and the areas of the epithelial defects were calculated. Treatment was considered effective for epithelial defect healing within two weeks, partially effective for

healing within two to four weeks and ineffective for healing requiring either more than one month or additional measures.[12 level II-3] The results showed that:

- Mean duration of epithelial defect before treatment was 7.2±6.3 weeks, and mean area was 7.86±7.32 mm^2.
- Umbilical cord serum therapy was effective in six eyes (42.9%), partially effective in six (42.9%), and ineffective in two (14.2%).
- Nevertheless, the epithelial defects in both the ineffective eyes were eventually healed within eight weeks.
- Mean healing time in effective or partially effective cases was 2.75±1.06 weeks.

The authors suggested that the use of umbilical cord serum eye drops for the treatment of persistent epithelial effect seems to be effective.

Vajpayee RB et al. did a randomised controlled trial to evaluate UCS eye drops therapy as a means of promoting the healing of persistent corneal epithelial defects. Sixty eyes of 59 patients with persistent epithelial defects were enrolled at random from the cornea service at Centre for Ophthalmic Sciences, New Delhi, India. Of 60 eyes of 59 patients enrolled, 29 were randomised to the AS eye drops group and 31 to the UCS eye drops group. One patient had both the eyes affected. Epithelial defects measuring at least 2 mm in linear dimension resistant to conventional medical management were included. Serial measurements of the size of the epithelial defects—namely, two maximum linear dimensions perpendicular to each other, and the area and perimeter was done at start of therapy and follow up days 3, 7, 14, 21. Rate of healing of the epithelial defects were measured as percentage decrease from the baseline parameter at each subsequent follow up.[13 level I] The results showed that:

- Of the 60 patients 48.3% (n=29) healed on either therapy; 58.06% (n=18/31) in the UCS group and 37.93% (n=11/29) in the AS group (p=0.19).
- The median percentage decrease in the size of the epithelial defect was significantly greater in the UCS group at days 7, 14 and 21 ($p< 0.05$) when measured in terms of the area and perimeter.
- The median time for closure of epithelial defects was 12.32 days in the AS group and 16.64 days in the UCS (p=0.18).
- A greater number of patients showed complete re-epithelialisation with umbilical cord serum (n = 18) than with autologous serum (n = 11) (p = 0.19).

From the study the authors suggested that UCS eye drops may be effective to faster healing of the persistent corneal epithelial defects refractory to all medical management compared to AS eye drops.

Erdem E et al. did a pre and post interventional study at the Balcali Hospital, Turkey to evaluate the role of UCS therapy in cases with persistent corneal epithelial defects (PED). Sixteen eyes of 14 patients with PED who were resistant to conventional treatment were treated with 20% UCS 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, 7^{th}, 14^{th} and 21^{st} days of treatment), and follow-up time was evaluated retrospectively.[14 level II-3] The results showed that:

- The mean size of epithelial defect on two perpendicular axes was 5.2×4.6-mm^2 (range: 2.5-8×2.2-9 mm^2). Mean duration of treatment was 8.3±5wk.

- UCS therapy was effective in 12 eyes (75%) and ineffective in four eyes (25%). The epithelial defects in four ineffective eyes were healed with amniotic membrane transplantation and tarsorrhaphy.
- The rate of complete healing was 12.5% by seven days, 25% by 14 days, and 75% by 21days.
- The healing time was prolonged in Grade III eyes in comparison to eyes in Grade I or Grade II.

This study has several limitations, including a small sample size, no control group, and its retrospective study design. One of its strengths was that patients were evaluated in respect to clinical severity of PED which may help clinicians to decide on treatment duration and efficiency at the presentation. Hence from the study, the author concluded that it was shown that the use of UCS eye drops seems to be an effective therapy in cases of early grade PED.

5.1.3 Treatment of Neurotrophic Keratitis

Yoon KC et al. in 2007 did a pre and post interventional study from Chonnam National University Medical School and Hospital, Gwang-Ju, South Korea, whereby twenty-eight eyes of twenty-eight patients with neurotrophic keratitis who were refractory to conventional treatment were treated with 20% UCS eye drops six to 10 times a day. Ophthalmic examinations including best-corrected visual acuity (VA) measurement, corneal sensitivity test, corneal fluorescein staining, and anterior segment photography were performed before and after the treatment. Concentrations of substance P, insulin like growth factor 1 (IGF-1), and nerve growth factor (NGF) in umbilical cord serum, normal peripheral blood serum, and tears were measured. Main outcome measures were epithelial healing time; changes of VA and corneal sensitivity after treatment; and levels of substance P, IGF-1, and NGF in umbilical cord serum, normal peripheral blood serum, and tears.[15 level II-3] The results were as follows:

- The epithelial defect healed completely in all eyes, with a mean healing time of 4.4±4.0 weeks.
- The epithelial defect healed within two weeks in eight eyes (28.6%), between two and four weeks in 14 eyes (50.0%) and after four weeks in six eyes (21.4%).
- After treatment, VA improved by >2 lines in 17 eyes (60.7%).
- Mean pretreatment corneal sensitivity was 21.1±10.5 mm, and mean post treatment corneal sensitivity was 24.3±11.7 mm (P<0.01).
- Mean concentrations of substance P, IGF-1, and NGF were 245.3±53.9 pg/ml, 239.0±77.1 ng/ml, and 729.7±72.0 pg/ml in umbilical cord serum; 169.5±81.0 pg/ml, 375.5±51.3 ng/ml, and 401.7±98.1 pg/ml in peripheral blood serum; and 69.8±24.9 pg/ml, 75.7±50.5 ng/ml, and 107.5±70.9 pg/ml in tears, respectively.

The authors suggested that UCS contains many neurotrophic factors, and hence UCS eye drops appeared to be effective for the treatment of neurotrophic keratitis.

5.1.4 Application of umbilical cord serum eyedrops in acute Ocular Chemical Burns

In 2011 Sharma N, et al. conducted a double-blind prospective RCT to evaluate the role of UCS therapy in cases of acute ocular chemical burns. Thirty three eyes of thirty two patients with acute ocular chemical burns of grade III, IV, and V severity were randomized into three groups: UCS eye drops (n = 12), AS eye drops (n = 11), and artificial tears (0.5%

HPMC+0.3% glycerin; n = 10). In addition, all eyes received standard medical therapy. The parameters evaluated were pain score, size, and area of epithelial defect, extent of limbal ischemia, corneal clarity, and symblepharon formation. The patients were followed up at day 1, 3, 7, 14, and 21 and at the end of months one, two, and three.[16 level I] The results were as follows:

- Mean time to complete epithelialization was 21.16 ± 26.81, 56.6 ± 35.5, and 40.13 ± 35.79 days in UCS, AS, and artificial tears groups respectively (p = 0.02).
- By day 21, the mean percentage decrease in epithelial defect diameter was 94.63 ± 11.99 with UCS compared with 53.17 ± 34.81 and 64.22 ± 42.43 with AS and artificial tears, respectively (p = 0.01).
- By month 3, the extent of limbal ischemia with UCS showed a mean percentage decrease of 73.43 ± 25.51 compared with 35.64 ± 25.60 and 43.71 ± 28.71 with AS and artificial tears, respectively (p = 0.008).
- More patients had clear corneas with UCS compared with AS and artificial tears (p = 0.048).
- No significant difference was seen between the groups with regard to symblepharon formation (p = 0.07).

The authors concluded that UCS therapy seems to be more effective than AS eye drops or artificial tears in ocular surface restoration after acute chemical injuries.

5.1.5 Application of umbilical cord serum eyedrops after laser epithelial keratomileus

Yoon KC et al. in 2011 reported an interventional study from Chonnam National University Medical School and Hospital, Gwangju, Korea whereby sixty patients (120 eyes) with myopia who underwent LASEK were studied. Thirty-two patients (64 eyes) were treated with 20% UCS eye drops in combination with conventional treatment (group A), and 28 patients (56 eyes) received conventional treatment only (group B). Epithelial healing time was analyzed. Visual acuity, refraction, haze score (0–4) and tear film and ocular surface parameters were evaluated at one, two, four and twelve weeks after LASEK. The concentration of transforming growth factor (TGF)-b1 in tears was measured with ELISA at one week after LASEK.[17 level II-3] The results were as follows:

- No significant differences in visual acuity and refraction were found between groups.
- The mean time to epithelial healing was 3.53 ± 1.19 days in group A (20% UCS eye drops in combination with conventional treatment) and 3.91 ± 1.41 days in group B (control; conventional treatment only) , p = 0.18.
- The mean haze scores at two and four weeks were 0.59 ± 0.80 and 0.31 ± 0.54 in group A and 1.06 ± 0.91 (p = 0.02) and 0.69 ± 0.78 (p = 0.03) in group B.
- Four and 12 weeks after LASEK, tear film break-up time was longer and keratoepitheliopathy score was lower in group A compared with group B.
- The mean concentration of TGF-b1 was lower in group A compared with group B (p = 0.01).

The authors concluded that application of 20% UCS eye drops in addition to conventional treatment after LASEK may reduce early postoperative corneal haze and improve tear film and ocular surface parameters.

5.2. SAFETY

Yoon KC et al. in 2006 did a an pre and post interventional study to investigate the therapeutic effect of UCS eye drops on dry eye associated with graft-versus-host disease (GVHD). Twenty-four eyes of twelve patients with severe dry eye syndrome associated with GVHD were treated with 20% UCS eye drops. There were no significant complications associated with the use of the eye drops were observed. [9 level II-2] From the study the authors suggested that UCS eye drops were safe.

Vajpayee RB et al. did a randomised controlled trial to evaluate UCS eye drops therapy as a means of promoting the healing of persistent corneal epithelial defects. Sixty eyes of 59 patients with persistent epithelial defects were enrolled at random from the cornea service at Centre for Ophthalmic Sciences, New Delhi, India. From the study none of the patients reported any side effects or discomfort with treatment. [13 level I] From the study the authors suggested that UCS eye drops were safe.

There was no retrievable FDA approval but in 2009, there was guidance for Industry entitled, “Minimally Manipulated, and Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications”. [18]

5.3. COST / COST-EFFECTIVENESS

There was no retrievable evidence on cost-effectiveness. In general, the pharmacy in United States charges USD$15 per 5 milliliter bottle of drops for AS eye drops, and the fee for the blood draw is about USD$10. A typical draw will deliver anywhere from six to eight bottles, so the charge is about USD$115.00 for the entire process. That should produce enough drops to last four to six months. In Europe the AS eye drops costs about €2.27 for 20% and €4.61 for 100% for a of a day dosage.[19] Costs range from USD$ 2.72 to USD$ 14.99 for product sizes ranging from 15 mL to 30 mL.[20] The estimated cost for 40 x 1ml of segmented UCS eye drops produced by the Cord Blood Bank Division, National Blood Centre is about RM152.20 (The estimation cost does not include labour cost, equipment charges and maintenance charges).

5.4. ORGANIZATIONAL

Umbilical cord blood can be collected after informed consent was obtained from the mothers.[4,5,9,11,12,17] After foetal delivery, about 60 to 80 ml of umbilical cord blood can be sampled from the umbilical cord vein.[1] Laboratory data for hepatitis B and C virus, syphilis and human immunodeficiency virus should be examined twice at 8 and 38 gestational weeks.[1,4,5,9,11,12] Tests to detect the presence of infection (hepatitis B and C virus, human immunodeficiency virus, TPHA, TOXO, CMV, HIV/HBV/HCV-NAT, HTLVI/II) should be performed at delivery.[10] Total quality system and good manufacturing practice facilities should be used.[10] Although no significant complications have been documented, potential adverse effects should always be considered when using UCS. Despite two laboratory examinations in pregnant donors, the possibility of transmission of blood-borne infections or blood-borne diseases cannot be absolutely excluded. In addition, bacterial contamination and allergy are other possible problems. Legal and regulatory issues as well as additional costs for serum preparation should also be considered before obtaining the serum.[1]

5.5. LIMITATIONS

This technology review has several limitations. The selection of studies was done by one reviewer. Although there was no restriction in language during the search but only English full text articles were included in this report.

6. CONCLUSION

From the above review it was found that there was fair to high level of evidence to show that UCS eye drops may have potential in the treatment of severe ocular surface diseases such as dry eye syndrome, corneal epithelial defect, neurotrophic keratitis, acute ocular chemical burns and after laser epithelial keratomileus. The majority of the studies were of controlled trials and interventional studies. However, most of the studies were limited by the small number of subjects and the short duration of study. Two randomised controlled trials comparing UCS eye drops versus AS drops showed better improvement using the UCS eye drops. From the studies the authors suggested that UCS eye drops were safe. The UCS eye drops manufacturing need to be done by a certified laboratory and personals who can handle the preparation. Issue of consent from patients who agree to donate cord blood, the testing for infectious diseases such as HIV, Hepatitis C, syphilis etc. also need to be addressed.

The estimated cost for 40 x 1ml of segmented UCS eye drops produced by the Cord Blood Bank Division, National Blood Centre is about RM152.20 for one patient (The estimation cost does not include labour cost, equipment charges and maintenance charges).

7. REFERENCES

1. Yoon KC. Use of Umbilical Cord Serum in Ophthalmology. Chonnam Med. Journal. 2014; 50:82-85. http://dx.doi.org/10.4068/cmj.2014.50.3.82
2. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International. Dry Eye WorkShop . Ocul Surf 2007; 5:75-92.
3. Gul A, Lone KP and Ahmad A. Implications of umbilical cord blood serum in clinical applications. theHealth. 2013; 4(4): 71-75
4. Yoon KC, Im SK, Park YG et al. Application of umbilical cord serum eyedrops for the treatment of dry eye syndrome. Cornea. 2006; 25:268-72.
5. Yoon KC, You IC, Im SK et al. Application of umbilical cord serum eyedrops for the treatment of neurotrophic keratitis. Ophthalmology. 2007; 114:1637-42.
6. Tsubota K, Goto E, Shimmura S et al. Treatment of persistent corneal epithelial defect by autologous serum application. Ophthalmology. 1999; 106:1984-9.
7. Cho PS, Messina DJ, Hirsh EL et al. Immunogenicity of umbilical cord tissue derived cells. Blood. 2008; 111:430-8.
8. Yoon KC, Im SK, Park YG, et al. Application of Umbilical Cord Serum Eyedrops for the Treatment of Dry Eye Syndrome. Cornea. 2006;Vol 25, Number 3:268-272
9. Yoon KC, Heo H, Im SK et al. Comparison of autologous serum and umbilical cord Serum eye drops for dry eye syndrome. Am J Ophthalmol. 2007; 144: 86–92.
10. Versura P, Profazio V, Buzzi M, et al. Efficacy of Standardized and Quality-Controlled Cord Blood Serum Eye Drop Therapy in the Healing of Severe Corneal Epithelial Damage in Dry Eye. Cornea. 2012; 0:1–7
11. Yoon KC, Jeong IY, Im SK et al. Therapeutic effect of umbilical cord serum eyedrops for the treatment of dry eye associated with graft-versus-host disease. Bone Marrow Transplantation. 2007; 39: 231–235. doi:10.1038/sj.bmt.1705566; published online 8 January 2007
12. Yoon KC, Heo H, Jeong IY et al. Therapeutic Effect of Umbilical Cord Serum Eye Drops for Persistent Corneal Epitheliali Defect. Korean Journal of Opthalmology. 2005; 19 (3): 174-178
13. Vajpayee RB, Mukerji N, Tandon R et al. Evaluation of umbilical cord serum therapy for persistent corneal epithelial defects. Br J Ophthalmol 2003; 87:1312–1316.
14. Erdem E, Yagmur M, Harbiyeli I, et al. Umbilical cord blood serum therapy for the management of persistent corneal epithelial defects, Int J Ophthalmol. 2014; 7(5): 807–810. doi: 10.3980/j.issn.2222-3959.2014.05.12
15. Yoon KC, You IC, Im SK et al. Application of Umbilical Cord Serum Eye drops for the Treatment of Neurotrophic Keratitis. Ophthalmology. 2007; 114:1637–1642.
16. Sharma N, Goel M, Velpandian T et al. Evaluation of umbilical cord serum therapy in acute ocular chemical burns. Invest Ophthalmol Vis Sci. 2011; 52(2):1087-92. doi: 10.1167/iovs.09-4170.
17. Yoon KC, Oh HJ, Park JW et al. Application of umbilical cord serum eyedrops after laser epithelial keratomileusis. Acta Ophthalmol. 2013; 91: e22–e28. doi: 10.1111/j.1755-3768.2012.02538.x
18. U.S. Department of Health and Human Services Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for Industry: Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for

Hematopoietic Reconstitution for Specified Indications. October 2009. MD 20852-1448, http://www.fda.gov/cber/guidelines.htm.
19. http://tec.sco.edu/autologous-serum-eye-drops.
20. Enzenauer RW, Kao A, Williams T et al. Costs of Various Preserved Artificial Tear Solutions for the Treatment of Dry Eye Conditions. Eye & Contact Lens. 2003; 29(4): 238–240

8. APPENDIX

8.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1948 to present

1. Severe ocular surface disease$.tw
2. "Ocul Surf" OR "ocular surface"
3. Dry eye syndrome.tw
4. Chemical burn$.tw
5. Corneal epithelial defect$.tw
6. Neurotrophic Keratitis.tw
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. Umbilical cord.tw.
9. Umbilical cord blood serum.tw
10. Human Umbilical cord blood serum.tw
11. Eye drops OR ophthalmic solution$.tw
12. Human Umbilical cord blood serum adj.2 eyedrops adj 1.tw
13. Treatment of severe ocular surface disease.tw
14. Therapy of severe ocular surface disease.tw
15. 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14
16. 6 AND 15

OTHER DATABASES

EBM Reviews - Cochrane Central Register of Controlled Trials	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Cochrane database of systematic reviews	
EBM Reviews - Health Technology Assessment	
EMBASE	

PubMeD

("umbilical cord"[MeSH Terms] OR ("umbilical"[All Fields] AND "cord"[All Fields]) OR "umbilical cord"[All Fields]) AND ("serum"[MeSH Terms] OR "serum"[All Fields]) AND ("ophthalmic solutions"[All Fields] OR "ophthalmic solutions"[MeSH Terms] OR ("ophthalmic"[All Fields] AND "solutions"[All Fields]) OR "ophthalmic solutions"[All Fields] OR ("eye"[All Fields] AND "drops"[All Fields]) OR "eye drops"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND ("patients"[MeSH Terms] OR "patients"[All Fields]) AND severe[All Fields] AND ("Ocul Surf"[Journal] OR ("ocular"[All Fields] AND "surface"[All Fields]) OR "ocular surface"[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields] OR "diseases"[All Fields])

8.2. Appendix 2

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris S2001)

Evidence Table: Efficacy / Effectiveness
Question: Is Umbilical Cord serum eyedrops effective for severe ocular surface disease

Bibliographic citation	Study Type / Method	LE	Number of patients and characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	comment
1. Yoon KC, Im SK, MD, Park YG, Jung YD et al. Application of Umbilical Cord Serum Eyedrops for the Treatment of Dry Eye Syndrome. Cornea 2006;Vol 25, Number 3:268-272	Pre and post interventional study. Fifty-five eyes of 31 patients with severe dry eye syndrome were treated with umbilical cord serum eyedrops. Symptom scoring, tear film break-up time (BUT), Schirmer test, corneal sensitivity test, and corneal fluorescein staining were performed before and 1 and 2 months after treatment, and conjunctival impression cytology was performed before and 2 months after treatment. The concentrations of epidermal growth factor (EGF), vitamin A, and transforming growth factor-A (TGF-A) in umbilical cord serum and normal peripheral blood serum were measured.	II-3	Fifty-five eyes of 31 patients with severe dry eye syndrome were studied. Patients with severe dry eye syndrome who were refractory to conventional treatments and had symptoms of dry eye for more than 3 months, low tear film break-up time (BUT, G5 seconds), low Schirmer test (5 mm), and positive fluorescein or rose bengal vital staining (Q3) were included. Twenty patients (38 eyes) of them had Sjo¨gren syndrome. Among 11 patients (17 eyes) who did not have Sjo¨gren syndrome, 6 patients (8 eyes) had chemical burns, 3 patients (6 eyes) had Stevens-Johnson syndrome, 1 patient (2 eyes) had cicatricial pemphigoid, and 1 patient (1 eye) had herpetic keratitis were included.	umbilical cord serum eyedrops.		2 months	Two months after treatment, significant improvement was observed ○ in symptom score (from 3.07 ± 0.54 to 0.96 ± 0.58), ○ tear film break-up time (BUT) (from 3.96 ± 1.56 to 5.45 ± 2.54 seconds), and ○ keratoepitheliopathy score (from 4.87 ± 3.22 to 1.71 ± 1.84) (P<0.01). ○ There was no statistically significant change in Schirmer and corneal sensitivity tests. ○ In impression cytology, the grade of squamous metaplasia (from 2.35 ± 0.72 to 1.44± 0.69) ○ and goblet cell density (from 80.91 ± 31.53 to 154.68 ± 43.06 cell/mm^2) improved significantly (P < 0.01). The mean concentration of EGF was 0.48 ± 0.09, TGF-A was 57.14 ± 18.98, and vitamin A was 230.85 ± 13.39 ng/mL in umbilical cord serum. The mean concentration of EGF was 0.14 ± 0.03, TGF-A was 31.30 ± 12.86, and vitamin A was 372.34 ± 22.32 ng/mL in peripheral blood serum. According to the authors, UCS serum contains essential tear components, and UCS eye drops may be effective and safe for the treatment of severe dry eye syndrome.	

Evidence Table: Efficacy / Effectiveness
Question: Is Umbilical Cord serum eyedrops effective for severe ocular surface disease

Bibliographic citation	Study Type / Method	LE	Number of patients and characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	comment
2. Yoon KC, Heo H, Im SK et al. Comparison of autologous serum and umbilical cord Serum eye drops for dry eye syndrome. Am J Ophthalmol 2007;144: 86–92.	Non-randomised controlled trial. To compare the therapeutic effect between autologous serum and umbilical cord serum eye drops in the treatment of severe dry eye syndrome.	II-1	Ninety-two eyes of 48 patients with severe dry eye syndrome (34 eyes of 17 patients with Sjögren syndrome and 58 eyes of 31 patients with non-Sjögren syndrome) were treated with either 20% autologous serum (41 eyes of 21 patients) or umbilical cord serum eye drops (51 eyes of 27 patients). Symptom scoring, corneal sensitivity test, tear film break-up time (BUT), Schirmer test, tear clearance rate (TCR), corneal fluorescein staining, and conjunctival impression cytologic analysis were performed before and one month and two months after treatment.	Umbilical cord serum eye drops	Autologous serum eye drops	2 months	Both autologous serum and umbilical serum treatments led to improvement in the symptom score, tear filmbreak up time (BUT), keratoepitheliopathy score, and impression cytologic findings. Changes of symptoms after autologous serum or umbilical cord serum eye drops with severe dry eye syndrome were as below: • Symptom score was lower at one month from 3.08±0.48 to 0.98 ± 0.55 for those treated with umbilical cord serum eye drops compared to autologous serum , from 2.98 ± 0.42 to 1.24± 0.64 (*P* = 0.03) • Symptom score was lower at two months from 3.08±0.48 to 0.94 ± 0.558 for those treated with umbilical cord serum eye drops compared to autologous serum , from 2.98 ± 0.42 to 1.20± 0.56 (*P* = 0.04) • Keratoepitheliopathy was lower at two month from 5.62 ± 3.19 to 1.75 ± 1.90 for those treated with umbilical cord serum eye drops compared to autologous serum , from 5.54 ± 2.84 to 2.34 ± 1.73 (*P* = 0.02) Changes of symptoms after autologous serum or umbilical cord serum eye drops with Sjögren syndrome were as below: • goblet cell density was higher at two months of umbilical cord serum treatment from 82.80 ± 29.41 to 150.25 ± 43.06 compared with autologous serum treatment from from 84.00 ± 39.33 to 120.93 ± 24.62 (*P =0* .04). The authors suggested UCS drops seems to be more effective in decreasing symptoms score and keratoepitheliopathy in severe dry eye syndrome and increasing goblet cell density in Sjögren syndrome compared with ASeye drops.	

Evidence Table: Efficacy / Effectiveness
Question: Is Umbilical Cord serum eyedrops effective for severe ocular surface disease

Bibliographic citation	Study Type / Method	LE	Number of patients and characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	comment
3. Versura P, Profazio V, Buzzi M, et al. Efficacy of Standardized and Quality-Controlled Cord Blood Serum Eye Drop Therapy in the Healing of Severe Corneal Epithelial Damage in Dry Eye. Cornea 2012; 0:1–7	Pre and post interventional study. The extent of epithelial defect was evaluated in square millimeters area, and subjective symptom score (Ocular Surface Disease Index score), Schirmer test I, break-up time, tear osmolarity, corneal esthesiometry (Cochet–Bonnet esthesiometer), conjunctival scraping, and imprint cytology with goblet cell count were performed at baseline (V0) and after 15 (V1) and 30 (V2, endpoint) days of treatment. Satisfaction and tolerability questionnaires were evaluated at V1 and V2.	II-3	Seventeen graft-versus-host disease (GVHD) and 13 Sjogren syndrome patients with severe persistent corneal defects were enrolled in the framework of a registered clinical trial (ClinicalTrials.gov NCT01234623).	Sterile UCS eye drops were prepared to supply 0.15 ng per eye per day epithelial growth factor and administered for 1 month in a 1-day dose dispensing.		30 days	Results: • A significant reduction was shown at the endpoint versus baseline in corneal epithelial damage (mean ± SD, 16.1 ± 13.7 vs. 40.9 ± 30 mm2/area, respectively), • discomfort symptoms (OcularSurface Disease Index score, 22.3 ± 10.3 vs. 39.3 ± 16.9), • scraping cytology score (3.8 ± 1.2 vs. 6.6 ± 2.1), and tear osmolarity (312.5 ± 7 vs. 322 ± 9.1 mOsm/L), • Whereas a significant improvement was shown in corneal esthesiometry (48.2 ± 2.1 vs. 49.7 ± 2.1 nylon/mm/ length, P , 0.05). • All patients reported a high degree of satisfaction upon drop instillation. The authors concluded that UCS eye drops represent a promising therapeutic approach in the healing of severely injured corneal epithelium and in subjective symptom relief.	

Evidence Table: Efficacy / Effectiveness
Question: Is Umbilical Cord serum eyedrops effective for severe ocular surface disease

Bibliographic citation	Study Type / Method	LE	Number of patients and characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	comment
4. Yoon KC, Jeong IY, Im SK et al. Therapeutic effect of umbilical cord serum eye drops for the treatment of dry eye associated with graft-versus-host disease. Bone Marrow Transplantation 2007; 39: 231–235. doi:10.1038/sj.bmt.1705566; published online 8 January 2007	Interventional study to investigate the therapeutic effect of umbilical cord serum eye drops on dry eye associated with graft-versus-host disease (GVHD).	II-3	Twenty-four eyes of 12 patients with severe dry eye syndrome associated with GVHD were treated with 20% umbilical cord serum eye drops. Symptom scoring, corneal sensitivity test, tear film break up time (BUT), Schirmer test, tear clearance rate (TCR), and corneal fluorescein staining were performed before and 2 and 6 months after treatment.	20% umbilical cord serum eyedrops.		6 months	Results: • Six months after treatment, significant improvement was observed in symptom score (from 3.83 ± 0.38 to 0.83 ± 0.57, $P < 0.01$), • corneal sensitivity (from 52.08 ± 6.06mm to 57.50± 3.00mm, $P < 0.01$), • tear film break up time (BUT) - from 2.50 ± 0.91 s to 5.71 ± 1.04 s, $P <0.01$), • and keratoepitheliopathy score (from 7.42 ± 2.02 to 1.29 ± 0.46, $P < 0.01$). There was no siginificant change in Schirmer test and TCR results. • No significant complications associated with the use of the eye drops were observed. The authors mentioned that from the study it was shown that Umbilical cord serum eye drops were safe and may be an effective way to treat severe dry eye associated with GVHD.	

Evidence Table: Efficacy / Effectiveness
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Bibliographic citation	Study Type / Method	LE	Number of patients and characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	comment
5. Yoon KC, Heo H, Jeong IY et al. Therapeutic Effect of Umbilical Cord Serum Eye Drops for Persistent Corneal Epitheliali Defect. Korean Journal of Opthalmology 2005; 19 (3): 174-178	Interventional study to evaluate the therapeutic effect of umbilical cord serum in the treatment of persistent epithelial defect of the cornea.	II-3	Fourteen eyes of 14 patients with persistent epithelial defect that had persisted for at least 2 weeks despite conventional treatment were treated with 20% umbilical cord serum eye drops six times a day. The images of the epithelial defects were captured using a camera attached to a slit lamp biomicroscope and the areas of the epithelial defects were calculated. Treatment was considered effective for epithelial defect healing within 2 weeks, partially effective for healing within 2 to 4 weeks and ineffective for healing requiring either more than 1 month or additional measures.	20% umbilical cord serum eye drops six times a day.		2 months	Results: • Mean duration of epithelial defect before treatment was 7.2±6.3 weeks, and mean area was 7.86±7.32 mm^2. • Umbilical cord serum therapy was effective in 6 eyes (42.9%), partially effective in 6 (42.9%), and ineffective in 2 (14.2%). • Nevertheless, the epithelial defects in both the ineffective eyes were eventually healed within 8 weeks. • Mean healing time in effective or partially effective cases was 2.75±1.06 weeks.	

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Bibliographic citation	Study Type / Method	LE	Number of patients and characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	comment
6. Vajpayee RB, Mukerji N, Tandon R et al. Evaluation of umbilical cord serum therapy for persistent corneal epithelial defects. Br J Ophthalmol 2003; 87:1312–1316.	RCT: To evaluate umbilical cord serum therapy as a means of promoting the healing of persistent corneal epithelial defects.	I	The study design was a prospective randomized controlled clinical trial. 60 eyes of 59 patients were divided into two groups, 31 in the cord serum group and 29 in the autologous serum control group. Epithelial defects measuring at least 2 mm in linear dimension resistant to conventional medical management were included. Serial measurements of the size of the epithelial defects—namely, two maximum linear dimensions perpendicular to each other, and the area and perimeter was done at start of therapy and follow up days 3, 7, 14, 21. Rate of healing of the epithelial defects were measured as percentage decrease from the baseline parameter at each subsequent follow up.	Umbilical cord serum	autologous serum drops	21 days	Results: • Of the 60 patients 48.3% (n=29) healed on either therapy; 58.06% (n=18/31) in the cord serum group and 37.93% (n=11/29) in the autologous serum group (P=0.19). • The median percentage decrease in the size of the epithelial defect was significantly greater in the cord serum group at days 7, 14 and 21 ($p< 0.05$) when measured in terms of the area and perimeter. • The median time for closure of epithelial defects was 12.32 days in the autologous serum group and 16.64 days in the cord serum group (p=0.18). • A greater number of patients showed complete re-epithelialisation with umbilical cord serum (n = 18) than with autologous serum (n = 11) (Pearson x = 0.19). • None of the patients reported any side effects or discomfort with either treatment. The authors concluded that Umbilical cord serum eye drops seems to lead to faster healing of the persistent corneal epithelial defects refractory to all medical management compared to autologous serum.	

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Bibliographic citation	Study Type / Method	LE	Number of patients and characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	comment
7.Erdem E, Yagmur M, Harbiyeli I, Hande Taylan-Sekeroglu H et al. Umbilical cord blood serum therapy for the management of persistent corneal epithelial defects, Int J Ophthalmol. 2014; 7(5): 807–810. doi: 10.3980/j.issn.2222-3959.2014.05.12	Interventional study to evaluate the role of umbilical cord blood serum (CBS) therapy in cases with persistent corneal epithelial defects (PED).	II-3	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, 7^{th}, 14^{th} and 21^{st} days of treatment), and follow-up time was evaluated retrospectively.	umbilical cord blood serum (CBS) eye dops		21 days	Results: • The mean size of epithelial defect on two perpendicular axes was 5.2×4.6-mm^2 (range: 2.5-8×2.2-9 mm^2). 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 7days, 25% by 14days, and 75% by 21days. • The healing time was prolonged in Grade III eyes in comparison to eyes in Grade I or Grade II. This study has several limitations, including a small sample size, no control group, and its retrospective study design. One of its strengths was 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. Hence the authors suggested that, from the study, it was shown that the use of CBS drops seems to be a safe and effective therapy in cases of early grade PED.	

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Bibliographic citation	Study Type / Method	LE	Number of patients and characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	comment
8. Yoon KC, In-Cheon You IC, Im SK et al. Application of Umbilical Cord Serum Eye drops for the Treatment of Neurotrophic Keratitis, Ophthalmology 2007;114:1637–1642.	pre and post interventional study	II-3	Twenty-eight eyes of 28 patients with neurotrophic keratitis who were refractory to conventional treatment. The patients with neurotrophic keraitis were treated with 20% umbilical cord serum eye drops 6 to 10 times a day. Ophthalmic examinations including best-corrected visual acuity (VA) measurement, corneal sensitivity test, corneal fluorescein staining, and anterior segment photography were performed before and after the treatment. Concentrations of substance P, insulinlike growth factor 1 (IGF-1), and nerve growth factor (NGF) in umbilical cord serum, normal peripheral blood serum, and tears were measured. *Main Outcome Measures:* Epithelial healing time; changes of VA and corneal sensitivity after treatment; and levels of substance P, IGF-1, and NGF in umbilical cord serum, normal peripheral blood serum, and tears.	umbilical cord serum eyedrops		5 weeks	Results: • The epithelial defect healed completely in all eyes, with a mean healing time of 4.4±4.0 weeks. • Theepithelial defect healed within 2 weeks in 8 eyes (28.6%), between 2 and 4 weeks in 14 eyes (50.0%), and after 4 weeks in 6 eyes (21.4%). • After treatment, VA improved by >2 lines in 17 eyes (60.7%). • Mean pretreatment corneal sensitivity was 21.1±10.5 mm, and mean posttreatment corneal sensitivity was 24.3±11.7 mm (P<0.01). • Mean concentrations of substance P, IGF-1, and NGF were 245.3±53.9 pg/ml, 239.0±77.1 ng/ml, and 729.7±72.0 pg/ml in umbilical cord serum; 169.5±81.0 pg/ml, 375.5±51.3 ng/ml, and 401.7±98.1 pg/ml in peripheral blood serum; and 69.8±24.9 pg/ml, 75.7±50.5 ng/ml, and 107.5±70.9 pg/ml in tears, respectively. The authors concluded that Umbilical cord serum contains many neurotrophic factors, and umbilical cord serum eye drops appeared to be effective for the treatment of neurotrophic keratitis.	

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Bibliographic citation	Study Type / Method	LE	Number of patients and characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	comment
9. Sharma N, Goel M, Velpandian T et al. Evaluation of umbilical cord serum therapy in acute ocular chemical burns. Invest Ophthalmol Vis Sci. 2011 Feb 25;52(2):1087-92. doi: 10.1167/iovs.09-4170.	Double-blind prospective randomized controlled clinical study. To evaluate the role of umbilical cord serum therapy in cases of acute ocular chemical burns.	I	33 eyes of 32 patients with acute ocular chemical burns of grade III, IV, and V severity were randomized into three groups: umbilical cord serum (n = 12), autologous serum (n = 11), and artificial tears (0.5% HPMC+0.3% glycerin; n = 10). In addition, all eyes received standard medical therapy. The parameters evaluated were pain score, size, and area of epithelial defect, extent of limbal ischemia, corneal clarity, and symblepharon formation. The patients were followed up at day 1, 3, 7, 14, and 21 and at the end of months 1, 2, and 3.	umbilical cord serum (n = 12),	autologous serum (n = 11), and artificial tears (0.5% HPMC+0.3% glycerin; n = 10).	3 months	Results: • Mean time to complete epithelialization was o 21.16 ± 26.81days in cord serum, o 56.6 ± 35.5 daysin autologous serum o and 40.13 ± 35.79 days in artificial tears groups (P = 0.02). • By day 21, the mean percentage decrease in epithelial defect diameter was o 94.63 ± 11.99 with cord serum o 53.17 ± 34.81 43 with autologous serum o 64.22 ± 42.43 with artificial tears (P = 0.01). • By month 3, the extent of limbal ischemia mean percentage decrease was o 73.43 ± 25.51 with cord serum o 35.64 ± 25.60 with autologous serum o 43.71 ± 28.71 with artificial tears (P = 0.008). • More patients had clear corneas with cord serum compared with autologous serum and artificial tears (P = 0.048). • No significant difference was seen between the groups with regard to symblepharon formation (P = 0.07). The authors concluded that Umbilical cord serum therapy seems to be more effective than autologous serum eye drops or artificial tears in ocular surface restoration after acute chemical injuries.	

Evidence Table: Efficacy / Effectiveness
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Bibliographic citation	Study Type / Method	LE	Number of patients and characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	comment
10. Yoon KC, Oh HJ, Park JW et al. Application of umbilical cord serum eyedrops after laser epithelial keratomileusis. Acta Ophthalmol. 2013: 91: e22–e28. doi: 10.1111/j.1755-3768.2012.02538.x	Interventional study from Chonnam National University Medical School and Hospital, Gwangju, Korea	II-3	Sixty patients (120 eyes) with myopia who underwent LASEK were studied. Thirty-two patients (64 eyes) were treated with 20% umbilical cord serum eye drops in combination with conventional treatment (group A), and 28 patients (56 eyes) received conventional treatment only (group B). Epithelial healing time was analysed. Visual acuity, refraction, haze score (0–4) and tear film and ocular surface parameters were evaluated at 1, 2, 4 and 12 weeks after LASEK. The concentration of transforming growth factor (TGF)-b1 in tears was measured with ELISA at 1 week after LASEK.	20% umbilical cord serum eye drops in combination with conventional treatment (Group A)	conventional treatment only (group B)	12 weeks	Results: • No significant differences in visual acuity and refraction were found between groups. • The mean time to epithelial healing was 3.53 ± 1.19 days in group A (20% umbilical cord serum eye drops in combination with conventional treatment) and 3.91 ± 1.41 days in group B (control-conventional treatment only) , p = 0.18. • The mean haze scores at 2 and 4 weeks were 0.59 ± 0.80 and 0.31 ± 0.54 in group A and 1.06 ± 0.91 (p = 0.02) and 0.69 ± 0.78 (p = 0.03) in group B. • Four and 12 weeks after LASEK, tear film break-up time was longer and keratoepitheliopathy score was lower in group A compared with group B. • The mean concentration of TGF-b1 was lower in group A compared with group B (p = 0.01). The authors concluded that Application of 20% umbilical cord serum eye drops in addition to conventional treatment after LASEK may reduce early postoperative corneal haze and improve tear film and ocular surface parameters.	