

PATIENT-REPORTED OUTCOMES – AN APPROACH AND APPLICATION IN AMNIOTIC MEMBRANE TRANSPLANTATION

Yana Manolova¹, Desislava Vankova², Christina Grupcheva¹

¹*Department of Ophthalmology and Visual Science, Faculty of Medicine,
Medical University of Varna*

²*Department of Social Medicine and Health Care Organization, Faculty of Public Health,
Medical University of Varna*

ABSTRACT

Patient-reported outcomes (PROs) are a comparatively novel concept in medicine and in public health services evaluation. It relies on the fact that medical technologies are not able to give all the information about the treatment or a medical condition. Some essential data can be obtained only from the patient.

Herewith, the PROs approach is presented in relation to amniotic membrane transplantation (AMT) which is applied to patients who have been treated at Varna Specialized Eye Hospital for different severe anterior ocular surface diseases (AOSDs).

The aim of the study is to present the PROs approach and the created especially for the study Patient-Reported Outcome Measures (PROMs) tool. Further on, we aim to summarize, analyze and discuss the PROs-data of the study.

MATERIALS AND METHODS: The presented PROs study enrolls 306 hospitalized patients diagnosed in seven cohorts and suitable for AMT for a period of seven years (2010-2016). It is a part of a wider research project. Demographic data and disease-related characteristics were collected in addition to the PROMs questionnaire. The PROMs instrument consists of 4 domains/questions, and the possible answers are arranged in ordinal scales. The first domain is Pain, and the possible answers are 5 (0 - none; 1 - sometimes low; 2 - always low; 3 - moderate to severe; 4 - always severe). The second domain is Photophobia, and the possible answers are 4 (0 - none; 1 - only at strong light; 2 - at daylight; 3 - at moderate light). The third domain is Secretion and the possible answers are 4 (0 - none; 1 - watery; 2 - mucous secretion; 3 - purulent discharge). The fourth domain is Hyperemia and the possible answers following the Efron grading scale are 5 (grade 0 - normal; grade 1 - trace; grade 2 - mild; grade 3 - moderate; grade 4 - severe).

RESULTS AND DISCUSSION: The AM treatment resulted in a significant reduction of the symptoms in all domains ($p < 0.001$). Regarding the Pain domain, in all the groups, over 60% of the patients reported improvement. More than 90% of the patients with the most severe conditions like keratitis reported improvement. The reported and analyzed results indicate that AMT has a positive impact on all the PROs do-

mains – Pain, Photophobia, Secretion and Hyperemia, for every patient ($p < 0.001$). This is a novel study for Bulgaria, which aims to measure the impact of AMT on PROs among a large number of patients with severe AOSDs divided into seven cohorts for seven years. AMT proved to be a surgical method for treatment of chronic, recurrent AOSDs that improve patients' subjective well-being.

Address for correspondence:

Yana Manolova
Specialized Eye Hospital
15 Doyran St
Varna, 9000
e-mail: y.m.manolova@gmail.com

Received: February 22, 2017

Accepted: March 14, 2017

Keywords: *patient-reported outcomes and measures, amniotic membrane transplantation*

INTRODUCTION

Patient-reported outcomes (PROs)

Medicine as a science and practice has changed tremendously during the last centuries but the human nature of the healing art has always been the care for the patient. In 1863, the legendary Florence Nightingale in her “Notes on Hospitals” (1) summarized “seven elements”, which are essential while evaluating the success of the curative process. One of these criteria is if the patient is “recovered or relieved” as a result of the hospital experience. During the years the importance of the subjective criteria in clinical medicine and in public health has increased. In 2009, the US Food and Drug Administration (FDA) (2) recommended that **PROs** be used as a desirable endpoint in the medical product development. Even though innovative technologies allow the measuring of physical, physiological or biochemical data of the patient, they are not able to provide all the data about the treatment or the disease. Some essential data can be obtained only from the patient.

Maybe the most famous definition of a “health outcome” is that of Donabedian (3) which states that a health outcome is the change of the current and the future health status of the patient that might be due to prior health care, including medication or surgery. FDA defines PROs as any report of the status of a patient’s health condition that comes directly from the patient, without an interpretation of the patient’s response by a clinician or anyone else. The outcome can be measured in absolute terms (e.g. severity of a symptom, sign, or state of a disease) or as a change from a previous measure.

Patient-Reported Outcome Measures (PROMs) are tools and/or instruments used to report PROs. Therefore, PROMs (i.e. a questionnaire plus the information and documentation that support its use) are a means to capture PROs data used to measure treatment benefit, risk in medical product clinical trials or public health services evaluation.

Amniotic membrane transplantation (AMT) is a surgical treatment, which could be successfully assessed by the application of PROMs. AMT is a surgical approach to manage severe anterior ocular sur-

face diseases (AOSDs). AOSDs are related to a damage of the anatomical and physiological features of eye structures - eyelids, tear film, conjunctiva, cornea and limbus. Disabilities associated with AOSDs very often create a vicious circle in which the individual protective mechanisms are not able to compensate and some irreversible processes like squamous metaplasia, cicatrization and vascularization lead to poor quality of life, reduced visual acuity and blindness. On the other hand, prolonged use of topical medications has its adverse effects related to the content of antibiotics, steroids and preservatives (4,5). In such cases, a mediator is needed, on one hand to protect the cornea, to be oxygen-permeable enough, while limiting the penetration and growth of toxic agents and for an anti-inflammatory effect, and on the other hand to stimulate the growth and differentiation of surface cells. Nowadays, an alternative option is called tissue engineering as a part of the regenerative medicine based on the concept of transplantation of exogenous and/or stimulation of endogenous factors and stem cells for the generation of organic substitutes and improvement of tissue function. One of the most important components of bioengineering is the support matrix, a role which the amniotic membrane (AM) fulfills. Its qualities are close to the perfect matrix (6-9). The first AMT was documented about 70 years ago. Subsequently, AM was established as a standard for the reconstructive surgery of the ocular surface (10,11). Today AM is widely used for reconstruction of the ocular surface as a treatment of serious corneal diseases such as corneal persistent, recurrent defects, corneal ulcers with or without descemetocoele and perforation (12-14), neurotrophic ulcer, microbial keratitis, band keratopathy (15), bullous keratopathy, after photorefractive keratotomy and LASIK, and chemical burns (16). It is used for ocular pemphigoid and the Stevens-Johnson syndrome (17-19). Other indications for AMT include reconstruction of the ocular surface such as conjunctiva surgery with various changes as squamous neoplasia, pterygium, symblepharon, reconstructive surgery of the fornices, stem cells deficit of the limb simultaneously with stem cell transplant, etc. (20). It acts as a “dressing” in various corneal pathologies. The am-

niotic membrane was recently used as a substrate for culturing limbal stem cells for transplantation.

The indications for AMT are many but the research reports and analysis on AMT and related PROMs are still scarce.

The aim of the study is to present the PROs approach and the created especially for the study PROMs tool. Further on, we aim to summarize, analyze and discuss the PROs data of the study.

MATERIALS AND METHODS

Settings and Sample

The presented PROs prospective study enrolls 306 hospitalized patients diagnosed and grouped into 7 cohorts suitable for AMT. It is a part of a wider research project on AMT. Demographic data and disease-related characteristics were collected in addition to the PROs questionnaire.

Methods

The PROMs instrument consists of 4 domains and the possible answers are put in ordinal scales. The first domain is **Pain**, and the possible answers are 4 (0 - none, 1 - sometimes mild; 2 - constantly mild; 3 - moderate to severe; 4 - constantly severe). The second domain is **Photophobia**, and the possi-

ble answers are 4 (0 - none, 1 - only at strong light; 2 - at daylight; 3 - at moderate light). The third domain is **Secretion** and the possible answers are 4 (0 - none, 1 - only tearing; 2 - mucous secretion; 3 - purulent discharge). The fourth domain is **Hyperemia** and the answers following the Efron grading scale are 5 (grade 0 - normal, grade 1 - trace; grade 2- mild; grade 3 - moderate; grade 4 - severe) (Table 1). Three time points measurement was done: pre-operatively (0 day), on the eighth day after surgery and on the 25th day. Patients fill in the PROMs instrument to assess subjective symptoms at each visit.

Statistical Analysis

The data was analyzed with SPSS v.20. To measure the significance, ANOVA on RANKS test with Student-Newman-Keuls Method has been applied and p-value below 0.05% was considered statistically significant.

RESULTS

All patients were transplanted cryopreserved AM type of filler or a combination technique (type of filler and coating). The patients were divided into seven cohorts according to their diagnosis. Table 2

Table 1. PROMs instrument for evaluation of the amniotic membrane application for anterior ocular surface reconstruction

Demographic data			
1. Sex: <input type="checkbox"/> male <input type="checkbox"/> female 2. Age: years.			
Clinical information			
3. Diagnosis of the patient:			
4. PROs	Pre-operatively	Postoperatively – 8 th day	Postoperatively – 25 th day
4.1. Pain: 0 – none; 1- sometimes mild; 2 – constantly mild; 3 – moderate to severe; 4 – constantly severe			
4.2. Photophobia: 0 – none; 1 – only at strong light; 2 – at daylight; 3 – at moderate light;			
4.3. Secretion: 0 – none; 1 – watery; 2 – mucous secretion; 3 – purulent discharge			
4.4. Hyperemia: 0 – normal; 1 – trace; 2 – mild, 3 - moderate; 4 – severe;			
5. Type of transplantation according to the depth and type of the defect of the cornea:			
<input type="checkbox"/> type – patch/onlay			
<input type="checkbox"/> type – graft/inlay: <input type="checkbox"/> one-layered <input type="checkbox"/> two-layered <input type="checkbox"/> multilayered			
<input type="checkbox"/> type – onlay on burning			

shows the distribution of patients according to their diagnosis.

Pain intensity is one of PROs, which determines the subjective quality of treatment. The results show that in the pre-operative period 75% of the patients experience moderate and constantly severe pain, while in the postoperative period the pain is significantly reduced as early as on the 8th day and persists until the 25th day ($p < 0.001$). The results of the effect after transplantation of AM on the 25th day show a significant reduction (over 60%) of pain in all cohorts of patients ($p < 0.001$). A maximum effect is observed in patients with postsurgical keratitis, with a reduction of pain with over 95%. Patients with virus keratitis follow them and then the cohort of patients with relapsed defects and those with neurotrophic ulcers (Figure 1).

While assessing **photophobia**, which is the second most important subjective factor for the patients, we take into consideration the significant difference in the pre-operative and postoperative period ($p < 0.001$). In the pre-operative period patients primarily complain of photophobia during daylight hours and in moderate illumination. Due to AMT on the 8th and 25th postoperative day they experience photophobia only in strong light. At the end of the studied period more than half of the patients reported absence of photophobia in the cohorts with postoperative keratitis - 83%, other diagnoses - 69%, bacterial keratitis - 67% and viral keratitis - 59%. In the other cohorts photophobia was reported only in strong light (recurrent and persistent corneal defects - 62%, injuries and burns - 58% and neurotrophic ulcers - 43%) ($p < 0.001$).

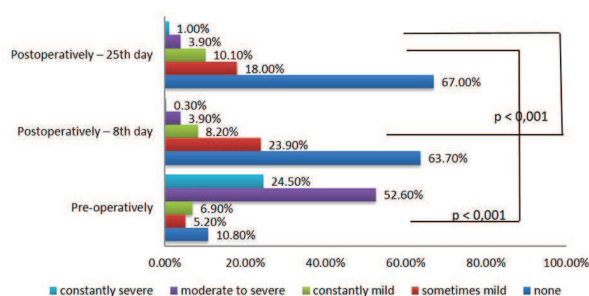


Fig. 1. Pain intensity improvement related to AMT. Preoperative and postoperative assessment on the 8th and 25th day: 0 - none, 1 - sometimes mild, 2 - constantly mild, 3 - moderate to severe, 4 - constantly severe

Secretion is another sign with subjective reflection. The results show that there is a significant difference in the patients' sensation in the pre-operative and postoperative period ($p < 0.001$), and between the sensation on the 8th and the 25th day after transplantation of AM ($p < 0.001$). In the pre-operative period, more than 60% of the patients

Table 2. Description of the sample according the diagnosis

DIAGNOSIS	NUMBER OF PATIENTS
1. Corneal persistent, recurrent defects:	66
Epithelial basement membrane dystrophy	21
Macular dystrophy	9
Peripheral ulcerative keratitis	3
Band keratopathy	9
Keratoconus	6
Keratoglobus	1
Corneal ulcers	17
2. Postsurgical keratitis:	30
Postoperative dellen (after pterigium)	2
Postoperative after LASIK	5
After PKP	5
Bullous keratopathy	18
3. Neurotrophic ulcers	38
4. Trauma and burns:	72
Trauma	42
Burns	30
5. Others:	19
Necrotizing scleritis	3
Symblepharon	2
After Tu conjunctivae	1
Steven-Johnson toxic epidermal necrolysis	3
Others	10
6. Bacterial keratitis	30
7. Viral keratitis:	51
Postherpetic	33
After adenoviral keratoconjunctivitis	18

experience tearing and mucus, most affected in the cohort of bacterial keratitis. On the 8th day only 19% of all cohorts report such symptoms, and on the 25th day only 9% experience tearing or the symptom is missing. The bacterial keratitis cohort is the one affected the most in regard to this symptom. On the 25th day there are patients from all cohorts who still have pyogenic secretion, 15% in the cohorts with injuries and burns, 6% in the cohorts with bacterial keratitis and in the other cohorts there are only a few cases ($p < 0.001$).

Hyperemia (red eye) is the last of the PROs. A moderate and severe form of hyperemia in the pre-operative period in more than 80% of the patients in all cohorts. A tendency towards reduction of the redness in the postoperative period on the 8th day after AMT is reported. For this short postoperative period a significant part of the patients had an average redness, more than 50% of the cohorts with postoperative keratitis and neurotrophic ulcers had mild redness ($p < 0.001$). Severe redness occurs in only 4% of the patients with burns and injuries and the patients with viral keratitis. A lack of redness was diagnosed in two cohorts - 21% in the cohort with recurrent or persistent corneal disorders and 20% of patients with viral keratitis. Moderate and severe redness was reported in only 6% of the patients on the 25th day ($p < 0.001$).

All the reported and analyzed results indicate that AMT has a positive impact on all the PROs domains for every patient ($p < 0.001$). This is the first study in our country, which aims to measure the impact of AMT on PROs among a large group of patients with different diagnosis over a seven-year period.

DISCUSSION

The results of this study demonstrate the important role of PROs and PROMs in the assessment of AMT in severely damaged anterior ocular surface. If chronic and recurrent AOSDs are not treated, there will be long-term pathological consequences for the patients. The inflammatory process leads to symptoms either directly (such as pain) or more indirectly (such as emotional and social problems), and also to long-term anterior ocular surface damage and blindness, which itself leads to symptoms such as pain and to disability.

Based on information gathered by filling out the card during the treatment, it was found that AMT has a strong effect on the subjective symptoms in patients with severe and chronically damaged ocular surface. The long period of research and the inclusion of patients with different diseases is a guarantee for representativeness and comparability of the results with those from the world practice of AMT. When treating eye surface diseases, pain relief is often a key outcome. However, pain cannot be quantified with objective clinical measures; PROMs are the only way to assess patients' subjective experience. In 2014, Stefaniu et al. described the effectiveness of applying AM in bullous keratopathy resulting from pseudophakic, aphakic and transplant rejection. The results of the study showed a lack of bullae within 1-2 weeks after the transplantation, as well as absence of pain, photophobia and tearing. Despite the recurrence of symptoms after the resorption of AM, a positive influence on PROs was reported in 88% of patients within a 4-year follow-up period (21). Srinivas et al. (2007) studied the effectiveness of AMT in regard to pain and additional indications in 7 patients (7 eyes) with bullous keratopathy and its role in reference to vision improvement in eyes with visual potential. The average follow-up period was 26.57 weeks. In 100% of the cases a full effect on pain was reported. In terms of the additional indicators: foreign body sensation, photophobia and tearing improvement were reported soon after the first postoperative day. An improvement in vision in 5 of the 7 patients (71.42%) was observed. The authors conclude that AMT is an effective alternative treatment of painful bullous keratopathy. Similar results in terms of pain were observed by other authors (22-24). In 2015, Tok et al. demonstrated in 15 eyes of 10 patients with toxic keratopathy after application of a topical anesthetic that the initially conducted conservative treatment was not effective because of the intense pain, persistent epithelial defects and progressive stromal thinning. For that reason the authors performed AMT, which led to a significant improvement in all cases except for two. In another publication in 2015, Sui et al. studied 21 eyes of 20 patients with bullous keratopathy and moderate pain was encountered pre- and postoperatively. They found that, postoperatively, 76% of the eyes experienced absolutely no pain,

while others complained of mild pain and 47% of the eyes remained asymptomatic for 3.6 months. In 2003, Espana et al. describe that they overcame 88% of the severe pain in the eyes with bullous keratopathy (25). These data suggest that AM plays an essential role in reducing the pain and the other subjective symptoms when the ocular surface has been damaged. In addition to the above-mentioned subjective indicators, AM plays a positive role on the inflammation processes and the hyperemia associated with them. The application of AM has a proven positive effect on the subjective sensation of redness (26). In 2005, Huang et al. showed that with patients with pterygium and AMT, the ocular surface recovers faster than in the cohort without AMT and both the levels of conjunctival hyperemia and the symptoms were lower (27). In 2016, Cheng et al. showed that the use of cryopreserved AM in patients with dry eye significantly affected the hyperemia for about 5 days and relieved the symptoms during the studied period which was four months (28). Our results based on PROs are in line with the published data, as we observed constant significant decrease of the redness upon AMT.

CONCLUSION

AMT proved to be a surgical method for treating severe anterior ocular surface disease that improves the patients' subjective well-being. The heterogeneity in the disease presentation, analyzed for 7 years pre- and postoperatively further enforces the above-mentioned statement regarding the favorable outcome of AMT in the growing range of AOSDs. The authors, being clinicians and public health researchers, are strong supporters of PROs application due to its patient- or person-centered approach. PROs employment is an effective way to assess the result of any health intervention. PROs have been increasingly recognized as part of the holistic approach to health, a necessary ingredient to comprehensive assessment of the impact of treatment and care. Practically, the PROs approach is a real-life personalized medicine.

REFERENCES

1. Nightingale F. Notes on hospitals [Internet]. London, Longman, Green, Longman, Roberts, and Green; 1863 [cited 2017 Feb 2]. 244 p.
2. FDA, 2009. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Label.
3. Donabedian A. Explorations in quality assessment and monitoring: the definition of quality and approaches to its assessment. Vol. 3. The methods and findings of quality assessment measurement and monitoring. Ann Arbor, MI: Health Administration Press; 1985.
4. Fraunfelder FT, Fraunfelder Jr FW, Chambers WA. Drug-Induced Ocular Side Effects: Clinical Ocular Toxicology. Elsevier Health Sciences; 2014. p. 425.
5. Honda R, Toshida H, Suto C, Fujimaki T, Kimura T, Ohta T, et al. Effect of long-term treatment with eyedrops for glaucoma on conjunctival bacterial flora. *Infect Drug Resist.* 2011;4:191–6. doi: 10.2147/IDR.S24250
6. Baguneid MS, Seifalian AM, Salacinski HJ, Murray D, Hamilton G, Walker MG. Tissue engineering of blood vessels. *Br J Surg.* 2006;93(3):282–90. doi: 10.1002/bjs.5256
7. Young CS, Abukawa H, Asrican R, Ravens M, Troulis MJ, Kaban LB, et al. Tissue-engineered hybrid tooth and bone. *Tissue Eng.* 2005;11(9–10):1599–610. doi: 10.1089/ten.2005.11.1599
8. Yang S, Leong KF, Du Z, Chua CK. The design of scaffolds for use in tissue engineering. Part I. Traditional factors. *Tissue Eng.* 2001;7(6):679–89. doi: 10.1089/107632701753337645
9. Walgenbach KJ, Voigt M, Riabikhin AW, Andree C, Schaefer DJ, Galla TJ, et al. Tissue engineering in plastic reconstructive surgery. *Anat Rec.* 2001;263(4):372–8. doi: 10.1002/ar.1117
10. Hao Y, Ma DH, Hwang DG, Kim WS, Zhang F. Identification of antiangiogenic and antiinflammatory proteins in human amniotic membrane. *Cornea.* 2000;19(3):348–52.
11. Kim JS, Kim JC, Na BK, Jeong JM, Song CY. Amniotic membrane patching promotes healing and inhibits proteinase activity on wound healing following acute corneal alkali burn. *Exp Eye Res.* 2000 Mar;70(3):329–37. doi: 10.1006/exer.1999.0794
12. Prabhasawat P, Tesavibul N, Komolsuradej W. Single and multilayer amniotic membrane transplantation for persistent corneal epithelial defect with and without stromal thinning and perforation. *Br J Ophthalmol.* 2001;85(12):1455–63. doi: 10.1136/bjo.85.12.1455

13. Solomon A, Meller D, Prabhasawat P, John T, Espana EM, Steuhl K-P, et al. Amniotic membrane grafts for nontraumatic corneal perforations, descemetocelles, and deep ulcers. *Ophthalmology*. 2002;109(4):694–703. doi: 10.1016/S0161-6420(01)01032-6
14. Takano Y, Fukagawa K, Miyake-Kashima M, Tanaka M, Asano-Kato N, Dogru M, et al. Dramatic healing of an allergic corneal ulcer persistent for 6 months by amniotic membrane patching in a patient with atopic keratoconjunctivitis: a case report. *Cornea*. 2004;23(7):723–5.
15. Anderson DF, Prabhasawat P, Alfonso E, Tseng SC. Amniotic membrane transplantation after the primary surgical management of band keratopathy. *Cornea*. 2001;20(4):354–61.
16. Meller D, Pires RT, Mack RJ, Figueiredo F, Heiligenhaus A, Park WC, et al. Amniotic membrane transplantation for acute chemical or thermal burns. *Ophthalmology*. 2000;107(5):980–9; discussion 990. doi: 10.1016/S0161-6420(00)00024-5
17. Tseng SC, Prabhasawat P, Barton K, Gray T, Meller D. Amniotic membrane transplantation with or without limbal allografts for corneal surface reconstruction in patients with limbal stem cell deficiency. *Arch Ophthalmol Chic Ill 1960*. 1998;116(4):431–41. doi:10.1001/archophth.116.4.431
18. Dua HS, Azuara-Blanco A. Allo-limbal transplantation in patients with limbal stem cell deficiency. *Br J Ophthalmol*. 1999;83(4):414–9. doi: 10.1136/bjo.83.4.414
19. Tsubota K, Satake Y, Ohyama M, Toda I, Takano Y, Ono M, et al. Surgical reconstruction of the ocular surface in advanced ocular cicatricial pemphigoid and Stevens-Johnson syndrome. *Am J Ophthalmol*. 1996;122(1):38–52. doi: 10.1016/S0002-9394(14)71962-2
20. LOP-Amniotic-Membrane-Transplantation.pdf [Internet]. [cited 2016 Jun 23]. Available from: <http://ibi-iran.com/wp-content/uploads/2015/07/LOP-Amniotic-Membrane-Transplantation.pdf>
21. Stefaniu G, Chitoroiu S, Secureanu F, Purcarea V, Zemba M. Use of amniotic membrane in bullous keratopathy palliative care. *J Med Life*. 2014;7(Spec Iss 2):88–91.
22. Tok OY, Tok L, Atay IM, Argun TC, Demirci N, Gunes A. Toxic keratopathy associated with abuse of topical anesthetics and amniotic membrane transplantation for treatment. *Int J Ophthalmol*. 2015;8(5):938–44. doi: 10.3980/j.issn.2222-3959.2015.05.15
23. Shimmura S, Shimazaki J, Ohashi Y, Tsubota K. Antiinflammatory effects of amniotic membrane transplantation in ocular surface disorders. *Cornea*. 2001;20(4):408–13.
24. Thatte S. Amniotic membrane transplantation: An option for ocular surface disorders. *Oman J Ophthalmol*. 2011;4(2):67–72. doi: 10.4103/0974-620X.83656
25. Espana EM, Grueterich M, Sandoval H, Solomon A, Alfonso E, Karp CL, et al. Amniotic membrane transplantation for bullous keratopathy in eyes with poor visual potential. *J Cataract Refract Surg*. 2003;29(2):279–84. doi: 10.1016/S0886-3350(02)01525-0
26. Liang W, Li R, Deng X. Comparison of the efficacy of pterygium resection combined with conjunctival autograft versus pterygium resection combined with amniotic membrane transplantation. *Eye Sci*. 2012;27(2):102–5.
27. Huang Y, Wang B, Ye Q. [Clinical study in combining application of mitomycin and amnion transplantation together with pterygium resection]. *Yan Ke Xue Bao Eye Sci Yan Ke Xue Bao Bian Ji Bu*. 2005;21(4):110–3, 123.
28. Cheng AMS, Zhao D, Chen R, Yin HY, Tighe S, Sheha H, et al. Accelerated Restoration of Ocular Surface Health in Dry Eye Disease by Self-Retained Cryopreserved Amniotic Membrane. *Ocul Surf*. 2016;14(1):56–63. doi: 10.1016/j.jtos.2015.07.003