Literature Review

Cultivated Limbal and Oral Mucosal Epithelial Transplantation in Severe Ocular Surface Disease

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ABSTRACT

Background: *To evaluate and compare the clinical outcome and safety of Cultivated Limbal Epithelial Transplantation (CLET) and Cultivated Oral Mucosal Epithelial Transplantation (COMET) in severe ocular surface disease.*
Methods: *Retrospective literature review. Studies reporting CLET or COMET as treatment of ocular surface disorder were included in this review. All studies were level IV or higher published between 2002 and 2012. The outcomes evaluated in each study include transplantation success rate, improvement of visual acuity, and the safety covered post operative complications. No publication data restriction was used.*
Results: *Eight articles were reviewed. Steven-Johnson Syndrome (SJS) was found to be the most common cause of ocular surface disease in all studies. None of these studies compared CLET and COMET directly. All studies achieved success rate and 3-years survival rate of more than 50%. Visual acuity improvement ranged between 43.5-67.8%, while the mean duration unitl epithelization ranged between 13.7 days to 3 months. The most common complication was persistent epithelial defect (PED).*
Conclusion: *Both CLET and COMET offer a viable and safe alternative in ocular surface reconstruction, and thus may be considered as the management of the ocular surface disorder following SJS or chemical injury.*

Keywords: *Cultivated limbal epithelium transplantation, cultivated oral mucosal epithelium transplantation, ocular surface disorder, ocular surface disease*

Severe ocular surface disease such as Steven-Johnson Syndrome (SJS) and ocular cicatrical pemphigoid (OCP), and thermal and chemical burns, are some of the most challenging entities to many ophthalmologists. Characrteristic of these disorders is the destruction of corneal epithelial stem cells in the limbus, which further results in conjunctivalization, neo-vascularization, chronic inflammation, and stromal scarring. As limbal stem cells were damaged or dysfunctional, a pathologic state known as limbal stem cell deficiency (LSCD) develops.[1,2,3]

Most patients with total LSCD have associated eyelid abnormalities and tear film disturbances. Aqueous and mucin tear deficiency, keratinization, and symblepharon further deteriorate the ocular surface.[1-4]

The management of ocular surface disorders with LSCD is often unsatisfying. The only definitive treatment for LSCD is limbal stem cell transplantation (LSCT). The main objective is to continue to supply a new corneal epithelium for a prolonged, if not indefinite, period of time to reduce the symptoms of ocular surface discomfort, photophobia and also to regain useful visual acuity.[1-4] A variety of surgical procedures have been developed over the last 30 years aimed at treating and reconstructing the damaged ocular surface epithelium.[1] As the prognosis after penetrating keratoplasty (PK) is poor for such diseases, the concept of ocular surface reconstruction has been developed via conjunctival transplantation, including limbal transplantation accompanied by amniotic membrane transplantation, dry eye treatment, and intensive immunosuppressive therapy.[1,5-8]

Over the course of the last decade, the cultivated technique of limbal transplantation has become increasingly popular, especially for the treatment of unilateral limbal stem cell deficiency. Cultivated limbal epithelial transplantation is believed to show promising results in the management of severe ocular surface disorders. Requirement of only small amounts of donor tissue and hence provide a better safety profile for the donor eyes has made this technique the preferred method of limbal transplantation, wherever suitable laboratory facilities are available. A recent technique of using cultivated tissue from oral mucosal epithelial as substitute is being developed, and was known as cultivated oral mucosal epithelial transplantation (COMET).[1,5,7]

Both CLET and COMET are still currently being studied regarding the efficacy and safety to the interventions. Up to this date, there is no review evaluating and comparing the success of transplantation in CLET and COMET.

METHODS

This is a retrospective literature review. A literature research was conducted through a search of Medline with Pubmed and Ophsource database using keywords cultivated limbal epithelium transplantation, cultivated oral mucosal epithelium trans-plantation and ocular surface disorder. All studies of level IV or higher, which reported patients with CLET or COMET in treating ocular surface disorder were included in the studies. Studies were excluded if the full text could not be obtained or if the article was not provided in English. The outcomes reported in each study were the success rate of the transplantation, improvement of visual acuity, and the complication after the transplantation. No publication data restriction was used.

RESULTS

There were 20 articles related to the keywords, but only 10 articles met the inclusion criteria. Two articles were excluded becase the full text articles were inaccesible. From the initial search results, 8 articles were included in this review, 4 articles used CLET and the remaining 4 articles used COMET.

The shortest mean follow up time was 20 months while the longest was 57.6 months. Steven-Johnson Syndrome was the most common cause of ocular surface disease in this review, except in studies by Basu *et al*[5] and Sangwan *et al*[6] where thermal or chemical injury is the leading cause. Among the thermal/chemical injuries, the most common is alkali injury.

All studies achieved success rate of more than 50%. The survival rate of transplantation were only shown in studies by Basu *et al*[5], Sangwan *et al*[6], Satake *et al*[9], and Hirayama *et al*[10], all of which showed a survival rate of more than 50% in 3 years follow up.

Visual acuity improvement ranged between 43.5-67.8%. It should be noted that the most studies performed keratoplasty as additional treatment, and the visual acuity improvement were measured after additional treatment had been performed. The mean duration until epithelization ranged between 13.7 days to 3 months. None of the studies mentioned the precise time duration of ocular surface stability except in both studies by Shimazaki *et al*[7,8] and in study by Inatomi *et al*[12] which stated that the mean duration until epithelization was 13.7 days, 19 days, and 3 months respectively. Other studies only stated that the ocular surface stability was achieved at their perspective mean follow up time.

The most common complication was persistent epitheliat defect (PED), which seemed to occur in eyes that already developed PED preoperatively. All studies did not explain the spesific management for the complications.

DISCUSSION

Limbal stem cells have an important role in the regular maintenance of the corneal surface epithelium. During normal homeo-stasis or in cases of injury, the activated stem cells from the limbus migrate centripetally to the central cornea and facilitate tissue regeneration.[21,22] When limbal stem cells are damaged or the limbal stem cell niche is dysfunctional, a pathologic state known as limbal stem cell deficiency (LSCD) develops. LSCD is typically characterized by the invasion of conjunctival epithelum onto the corneal surface leading to conjunctiva-lization, neovascularization, subepithelial scarring and symblepharon formation; these result in corneal opacity and visual impairment and varying degrees of discomfort, including redness, irritation, and watering in the affected eye.

Management of LSCD depends on the extent of involvement (partial or total), laterality (unilateral or bilateral), severity of ocular surface inflammation, presence of symblepharon, tear status, ocular surface keratinization, and systemic factors such as age and general health of the patient. The only definitive treatment for LSCD is limbal stem cell transplantation (LSCT). Novel surgical modalities have been developed over the past 20 years, aimed at the reconstruction was first introduced via an autologus conjunctival transplantation for unilateral chemical injury reported in 1977.[14,16,22] Thereafter, kerato-epithelioplasty and auto-grafts or allografts of limbal transplantations were developed to improve the outcome of ocular surface reconstruction. Over the past decades, cultivated limbal stem cell transplantation has been shown to be a promising treatment modality in the management of severe limbal stem cell deficiency.

Since severe ocular surface disorders are mostly bilateral, the opt for allogenic limbal epithelial transplantation was needed, resulting in intensive, prolonged post operative immune-suppresive therapy which is necessary for the prevention of allograft rejection.[1,14,16] This markedly reduces the quality of life of the patients and severely affects clinical outcomes. These drawbacks have led to investigation as to whether the ocular surface could be reconstructed by using an autologus mucosal epithelium of non-ocular surface origin. Epithelial cells isolated from the oral mucosa are generally thought to be at a lower stage of differentiation than skin keratocytes and offer the following potential advantages: short cell turnover time with resultant short culture time requirement and long-term maintenance under culture conditions without keratin-ization. Moreover, the oral mucosa is an ideal location for tissue biopsy, because the resultant scar is inconspicuous.

The main objective of cultivated epithelial transplantation is to continuously provide new corneal epithelium for a prolonged, if not indefinite, period of time so that patients can be relieved from irritating symptoms such as photophobia.[2,4] With combination of other surgeries such as keratoplasty, patients are expected to regain useful visual acuity.

Based on this review, the most common etiology was SJS except in studies by Basu *et al*[5] and Sangwan *et al*[6] where thermal/chemical injury is the leading cause. This corresponds to other studies that mentioned SJS as one the most common etiology for LSCD, as it is common in Eastern Asia.

Criteria defining clinical success of cultivated epithelial transplantation had not been clearly described and varied widely. Success had been defined as improvement of corneal vascularization, conjunctivalization, inflammation, epithelial defect, photophobia, and pain. Improvement of corneal epithelial transparency, integrity, and stability had been reported as clinical success in more than 50% of patients.[7-10] In this review, the success rate for CLET ranged from 59.3% to 71.4% at a follow up time ranged from 18 months to 57 months, while the success rate for COMET reaches up to 100% in studies by Sotozono *et al*[9] and Inatomi *et al*[11] with a mean follow up time of 28.7 months and 20 months respectively. Unfortunately, none of the studies mentioned the duration between the time of surgery to the achievement of the success.

Primary failure may occure due to unsuccessful cultivation. Stem cell fail gradually due to acute or chronic immuno-logic rejections and/or offending mechanisms including exposure, tear film instability, cicatrical entropion/ectropion, trichiasis, symblepharon, shallow fornices, and improper stem cell niche. Exposure, dry eye, and ongoing inflammation are the main risk factors for survival of stem cell grafts. Progressive conjunctivalization may be attributable to gradual cell attrition and final failure.[12,13] Only 3 studies reported the survival rate of each treatment, with promising results of up to 67.5% and 70% 3-years-survival in CLET and COMET respectively. Visual acuity improvement of at least two lines was found in more than 50% cases. It should be noted that the visual acuity was reported after additional surgeries were performed, mostly keratoplasty. Post operative visual acuity seemed to be related to the presence of corneal opacity.[8,14]

Complications after both CLET and COMET are common, with PED as the most common complication. PED ranged between 7.1% to 37% in CLET and 7.5% to 34.8% in COMET. Unfortunately, the management of the complications was not explained in details. The possibility of PED occurrence increased in eyes with preexisting PED before intervention. The severity of other abnormalities such as lid abnormalities and tear insufficiency might also affect the occurrence of post operative PED.[2-5]

CONCLUSION

Based on this review, both CLET and COMET offers a viable and safe alternative in the reconstruction of a stable ocular surface, and therefore might be considered as a management in ocular surface disorders following SJS or chemical injury. Due to variation of mean follow up times and number of subjects between the two treatments, it is not possible to conclude which of the two procedures provide better result.

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