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Therapeutic Potential of Limbal Mesenchymal Stem Cell Secretome for Repair Ocular Surface in Experimental of Dry Eye Disease

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Abstract

Background: The objective of this study to explain relationship limbal mesenchymal stem cell secretome (L-MSC) for repair ocular surface in experimental model of dry eye disease (DED)

Methods: The research design used experimental study. Pre and post experimental study composed of topical instillation of limbal mesenchymal stem cell secretome group, balance salt solution (BSS) group, and normal control group.

Result: Topical instillation of limbal mesenchymal stem secretome improved regeneration of corneal epithelial cell ($p > 0.05$) and promoted goblet cell restoration ($p = 0.016$)

Conclusion: In conclusion, topical instillation of limbal mesenchymal stem secretome has potential regenerist therapy to preserve ocular surface in experimental DED model

Keyword: limbal mesenchymal stem cell; secretome; dry eye disease

1. Introduction

Dry eye disease is a chronic ocular condition and significantly impacts visual function with multifactorial origin. In recent years, the epidemiology of DED is increased. The incidence and prevalence in Asia is higher than in Europe and America suggesting racial factor are involved in dry eye etiology [1]. In Indonesia, the majority of DED is 37,6 % by 40-49year age group and 1,4 times higher for men than women [2].

Defect on tear film components due to oxidative stress lead ocular surface epithelial exposed triggered inflammatory process. Recently, the management of DED is supportive. Application of artificial tears, topical anti-inflammatory, and immunosuppressant is standard therapy for DED. However, the results obtained less optimal. Mesenchymal stem cell is characterized non-hematopoietic, multipotent progenitor cell, and morphology like fibroblast [3]. In particular, Limbal MSC have been shown to encourage the regeneration of corneal epithelial cells derived from limbal tissue biopsies. However, availability and cultivation of healthy donor remain challenges such as limited sources. Secretome originated from mesenchymal stem cell that contain wide variety of bioactive substances, soluble factor, growth factor, and anti-inflammatory[3],[4]. In the future, secretome has a potency as a candidate acellular regenerative therapy that promises in management ocular surface disease including DED.

2. Subjects and Methods

2.1 Animal model

A total of 30 New Zealand white rabbit were randomly divided into three groups. Twenty rabbits induced with intraperitoneal injection of xylazine-ketamine. The operation were performed under sterile condition. Resection of the partial inferior lacrimal gland combined with interglandular injection of 300 µg Concanavalin A (Con A; Sigma-Aldrich) diluted in 20 ul PBS using a Hamilton syringe with a 33 gauge needle were performed to create animal model. Five days after induction, the schirmer tear test and corneal fluorescein test was examined. The schirmer tear test less than 4 mm was included in this study [5].

2.2 Secretome limbal mesenchymal stem cell

The cell was obtained from the stem cell laboratory, Universitas Airlangga. To obtain secretome, amount of 5×10^3 cell/well of L-MS-C was treated for 24 hours using media composed of α -MEM, 1% amphotericin B, 1% NEAA, 1% penicillin-streptomycin, and 2 % FBS). The secretome was collected and filtered using 0.45 um millipore, the osmolarity and acidity were adjusted for 270-300 mOsm/L and 7.2-7.5, respectively. The secretome was packaged into single dose application in sterile eppendorf tube and stored at -20°C until further application

2.3 Corneal fluorescein dye staining

Using sodium fluorescein test strips instill into the inferior lateral conjunctival sac. The corneal surface was observed in the portable slit lamp, cobalt blue light, and zoom 16 times. The picture was taken using camera (Canon, A2500, 16 Megapixel) and analyzed using image J (v1.48) in 3 times by independent observer

2.4 Goblet cell density

Exenteration procedure was performed and stored in formalin. The histopathology section sliced in 4 µm and subjected to hematoxylin eosin staining. Using Nikon H600L microscope under 400x magnification goblet cell density was observed. The characteristic of goblet cell are rounded and plump. Goblet cell density was counted using cell count Nikon Image system. The result was validated by an anatomic pathologist.

2.5 Statistical analysis

The data was processed using SPSS version 21.0 where $P < 0.05$ was considered to be statistically significant. Statistical measures presented in descriptive table (e.g mean and standard deviation). Statistical analysis between group was analyzed with Kruskal Wallis variance analysis and independence T-test

3. Results

3.1 Limbal mesenchymal stem cell secretome promote regeneration of corneal epithelial cell

L-MS-C secretome promote regeneration of ocular surface on day 7 compared to BSS control group (Figure 1). The fluorescein dye staining area on L-MS-C group markedly decreased ($2.88 \times 10^5 \pm 7.98 \times 10^4$ pixel) compared to BSS control group ($1.08 \times 10^6 \pm 1.05 \times 10^4$ pixel) (Table 1).

Table 1. The effect instillation L-MS-C to repair ocular surface

Treatment Group	n	Fluorescein dye staining area Day-0 (Pixel)	Fluorescein dye staining area Day-7 (Pixel)	p
L-MS-C secretome	10	$8.15 \times 10^6 \pm 3.67 \times 10^4$	$2.88 \times 10^6 \pm 8.51 \times 10^4$	$<0.001^*$
BSS	10	$7.98 \times 10^5 \pm 2.09 \times 10^4$	$1.08 \times 10^5 \pm 1.05 \times 10^4$	$<0.001^*$
p		0.377	<0.001	

*independence T-test

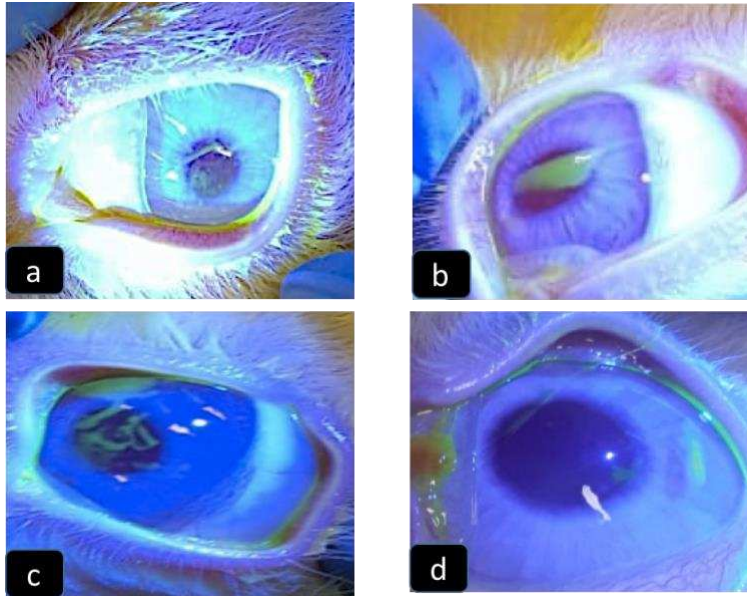


Figure 1: Topical instillation of L-MSC secretome promoted corneal epithelial regeneration. (A). Fluorescein dye staining in BSS group day 0; (B). L-MSC secretome group day 0; (C) BSS group day 7; D L-MSC secretome group day 7. Green staining: Fluorescein staining in corneal epithelial defect.

3.2. Instillation of Limbal MSC secretome repaired of goblet cell

The conjunctival goblet cells has important role to secreting mucin. The musin has a role involving in formation tear film. In this study, goblet cell density count was significantly higher in the eyes with topical instillation of L-MSC secretome (2.54 ± 0.69 cells/ visual field, $p=0.016$) compared to the BSS control group (Table 2, Figure 2).

Table 2. The effect instillation L-MSC to restored of goblet cell in conjunctiva

Group	n	Goblet cell density (cell/visual field)	p
L-MSC Secretome	10	2.54 ± 0.69	
BSS	10	0.98 ± 0.24	$<0.016^*$
Normal control	10	13.12 ± 2.50	

*(One Way ANOVA, Tukey post-hoc test)

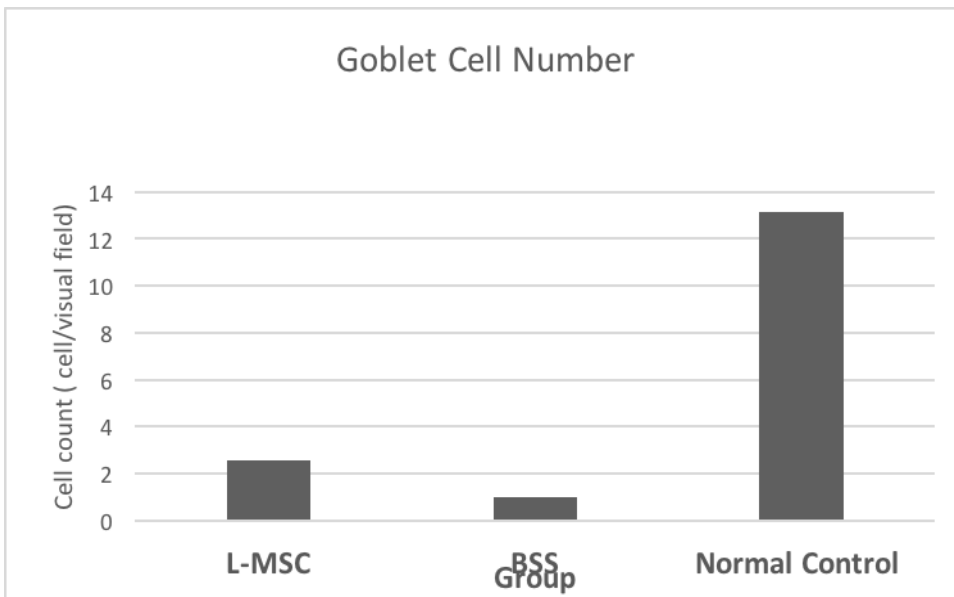


Figure 2. The graph showed goblet cell density among group

4. Discussion

Dry eye disease is a chronic ocular condition and significantly impacts visual function with multifactorial origin [6],[7]. It is characterized by tear instability and inflammation on the ocular surface. The growth factor such as epidermal growth factor (EGF) and keratinocyte growth factor (KGF) has important role to repair and regenerate ocular surface[8],[9]. Stem cell secretome has various growth factor might have beneficial effect on ocular surface regeneration. In severe dry eye disease, there is epithelial damage on corneal surface.

In this study, topical instillation of L-MSc secretome successfully promote corneal epithelial regeneration. In line with this study, other study demonstrated that secretome derived from limbal fibroblast had therapeutic effect such as promote limbal stem cell proliferation and differentiate into corneal epithelial in mouse model of limbal stem cell deficiency [10]. Some studies showed the regeneration of corneal wound healing after instillation MSC secretome by cell to cell interaction and surrounding tissue mechanism such as proliferation, differentiation, communication, and migration [11],[12].

The primary mechanism of dry eye disease associated with tear film abnormalities. The tear film is composed of three main layers. The outermost layer is formed predominantly of lipid, which function is to prevent water evaporation and reduce the tension of the ocular surface. The middle is an aqueous layer and plays a role in protecting against pathogens and particle and hydration ocular surface [13],[14]. Its contain insoluble and soluble component such as proteins, electrolytes, peptides, and small molecules. The innermost layer is a mucin layer that resides directly at the surface of the cornea. Mucin originated from the goblet cell. Goblet

cell loss in the conjunctival epithelium decreased concentration of mucin in tear film and correlate with DED symptom.

In this study, instillation of limbal MSC secretome preserved of goblet cell. In line with this study revealed there were increased number of goblet cell in conjunctiva epithelium after topical instillation of bone marrow mesenchymal stem cell in experimental dry eye model[15]. Another study, instillation of human uterine cervical stemcell secretome in rat model of dry eye disease revealed increased corneal epithelial wound healing process[16]. There are limited report of studies using topical L-MSC secretome in ocular surface particularly in DED. The secretome is composed growth factor, soluble factor, microvesicles that have role in wound healing process and promising as regenerative study.

Limitation on this study, the exact content of the secretome has yet determined, further studies are mandatory to analyze composition of the L-MSC secretome.

5. Conclusion

In conclusion, topical instillation of limbal mesenchymal stem secretome has potential effect regenerist therapy to preserve ocular surface in experimental DED model.

6. Acknowledgement

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8. Conflict of Interest

Nil.

9. Ethical Satandard

Ethical approval was obtained from Institutional Ethical Committee of Faculty of Veterinary medicine, Universitas Airlangga (No: 2.KE.053.06.2020). All Proseures performed with ethical standards.

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