의학석사 학위논문

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지도교수 현 준 영

이 논문을 의학석사 학위논문으로 제출함

2014 년 4 월

서울대학교 대학원

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김 동 현

김동현의 의학석사 학위논문을 인준함

2014 년 7 월

위 원 장 김 태 우 (인)

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ABSTRACT

Purpose: To evaluate whether cell migration or enlargement is the main mechanism of initial endothelial cell recovery following cataract surgery

Methods: A prospective observational study of 24 patients aged 50–80 years who were diagnosed with moderate cataract and received uncomplicated phacoemulsification with a 2.75-mm temporal clear corneal incision, was performed in Seoul National University Bundang Hospital. The values of endothelial cell density(ECD) and cell area were obtained in central and 4 paracentral (superior, inferior, nasal, and temporal) locations using non-contact specular microscopy. ECD, cell area, the divisional proportion of ECD (DPECD = ECD in each location/the sum total of ECD), the transition of endothelial cell area relative to preoperative average cell area (TECA), and the coefficient of variation of endothelial cell area(CV) in each location were investigated pre- and 1 day, 1 week, and 4 weeks postoperatively.

Results: ECD significantly decreased 1 day, 1 week, and 4 weeks postoperatively ($p = 0.010$, 0.015, and 0.003, respectively), and the cell area increased ($p = 0.008$, 0.013, and 0.002, respectively) in the temporal location. Postoperative DPECD decreased, TECA and CV increased only in the temporal area significantly, compared to preoperative values. There were no significant differences at other locations between pre- and postoperative ECD, cell area, DPECD, TECA and CV.

Conclusion: Postoperative changes of ECD, cell area, DPECD, TECA, and CV were limited to the temporal area adjacent to the primary corneal incision. Cellular enlargement, rather than cell migration, may underlie the endothelial cell recovery after phacoemulsification.

Keywords: phacoemulsification, corneal endothelial cell, cellular migration, cellular enlargement, endothelial cell recovery mechanism

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INTRODUCTION

A lot of studies have examined the changes in central corneal endothelial cells density(ECD) after phacoemulsification until now.[1-4] It is widely known that damages of corneal endothelium are recovered by cellular migration and enlargement.[5] However, the mechanisms involved in endothelial recovery have not been fully determined. Corneal endothelial cell(CEC) change and recovery mechanism after endothelial damages have been studied for several decades, and most subjects of in vivo studies about the CEC recovery mechanism following endothelial damages were animals including rabbit, rat or monkey.[6-9] Human CEC recovery mechanism have been studied mostly in vitro or ex vivo because human in vivo study is very difficult to perform.[10-17] Human in vivo studies about CEC recovery mechanism following endothelial damage were rare. Hughes et al. showed the rise in central ECD increase after toxic endothelial injury which might represent cellular migration from less affected area,[14] and Jacobi et al. provided the evidence to support the hypothesis that the grafted endothelial cells migrated onto the host tissue after descemet membrane endothelial keratoplasty.[18]

To our knowledge, there is no human in vivo study for evaluating CEC recovery mechanism after phacoemulsification. Perhaps the main recovery mechanism will be cellular migration or enlargement. We hypothesized that the proportion of ECD in each location to the sum total of ECD in central and 4 paracentral locations would change pre- and postoperatively, if the endothelial healing is mainly done by cellular migration, but the proportions would be almost fixed except directly damaged location and endothelial cell area in damaged location would be enlarged, if enlargement affects mostly (Figure 1). In the present study, we investigated the main mechanism of early endothelial recovery after phacoemulsification by analyzing the divisional proportion of endothelial cell density (DPECD) in central and 4 paracentral (superior, inferior, nasal, and temporal) areas and the transition of endothelial cell area relative to preoperative average corneal endothelial cell area (TECA) of 5 locations postoperatively.

MATERIALS AND METHODS

This prospective observational study was conducted at the Seoul National University Bundang Hospital from November 2008 to April 2009. Patients aged 50 to 80 years diagnosed with moderate cataract were enrolled. Exclusion criteria were as follows: previous corneal disease, corneal trauma, or intraocular surgery; glaucoma or uveitis; pseudoexfoliation syndrome; use of contact lenses; intraoperative complications (posterior capsule rupture with or without vitreous loss); and diabetes mellitus. The institutional review board of Seoul National University Bundang Hospital approved the study protocol (IRB number: B-0909/083-020), and the protocol complied with the tenets of the Declaration of Helsinki. After obtaining informed consent, each patient received a standard preoperative ocular examination. Cataracts were graded according to the Lens Opacities Classification System III (LOCS III).

Surgeries were performed using the Infiniti vision system (Alcon Laboratories, Inc., USA) by a single experienced surgeon (Hyon JY). All patients received 0.5% proparacaine hydrochloride topical anesthesia preoperatively. A 2.75-mm clear corneal incision was made on the temporal

side. A side incision was made 90 °clockwise to the main incision. A routine phaco-chop technique with torsional mode was used at a 40% amplitude, 400 mmHg vacuum limit, and a 40 mL/min aspiration flow rate. A single-piece hydrophobic foldable intraocular lens (SN60WF, Alcon, USA) was implanted into the capsular bag. No sutures were required on the corneal wound. Cumulative dissipated energy (CDE) was measured intraoperatively.

The endothelial cell images were obtained from noncontact specular microscopy (Noncon Robo SP-8000 noncontact specular microscope, Konan, Japan) by a single experienced examiner. The endothelial cell density and cell area were also calculated with the Konan computer-assisted analysis program using the center method by a same examiner. The endothelial cells in the obtained image were counted as many as possible to minimize. Before examination, patients' head positions were checked not to be tilted. Endothelial cells in central and four paracentral locations 3 mm away (superior, inferior, nasal, and temporal) were examined by consistently changing the microscope fixation target.

Ciprofloxacin (Cravit®) and 0.1% prednisolone acetate (Flarex®) were

prescribed for three weeks postoperatively. The patients were examined with specular microscopy preoperatively and 1 day, 1 week, and 4 weeks postoperatively. DPECD in each location was calculated by dividing each divisional ECD by the sum total of ECD in five locations. To calculate the transition of endothelial cell area relative to the preoperative average cell area (TECA), each calculated cell area was divided by the preoperative average endothelial cell area in each location. The coefficients of variation(CV) of endothelial cell area in each location were also investigated pre- and postoperatively for analyses of corneal endothelial dysfunction and variations of cell area. To evaluate a possible endothelial damage of the side incision, the ECD and cell area were analyzed according to laterality additionally.

Data were analyzed using SPSS 18.0 software (SPSS Inc, Chicago, IL). Comparison between each division was performed using one-way ANOVA. The postoperative changes in each division were evaluated using repeat measure ANOVA and paired *t* test; $p < 0.05$ was considered statistically significant. The significant p value limit was modified according to Bonferroni's correction method to address problems caused by multiple

comparisons.

RESULTS

In total, 24 eyes (13 right and 11 left) of 24 patients (9 men and 15 women) aged 68.1 ± 10.0 (SD) years (range 51 to 80 years) underwent surgery. The mean nuclear opalescence grade was 2.29 ± 0.53, and mean CDE was 7.07 ± 4.14.

Table 1 summarized the preoperative mean endothelial cell density and area. There were no significant differences of ECD and cell area in the central and 4 paracentral locations. DPECD was most in superior and least in inferior paracentral location. The sum of ECD of 5 locations in postoperative 1 day, 1 week, and 4 weeks, were significantly decreased when compared with preoperative sum of ECD (Figure 2). A preoperative sum of ECD was 12854 ± 2145 cells/mm^2, and postoperative 1 day, 1 week, and 4 weeks sum of ECD were 12305 ± 1847, 12209 ± 1858, and 11988 ± 1812 respectively. (p=0.014, 0.001, 0.002, repeat measure ANOVA) Figure 3 illustrated the changes of the ECD and average endothelial cell area according to location pre- and postoperatively. The endothelial cell density was decreased and the cell area was increased significantly in temporal location according to time progression

(ECD: p = 0.010, 0.015, 0.003; cell area: p = 0.008, 0.013, 0.002; postoperative 1 day, 1 week, and 4 weeks respectively, repeat measure ANOVA), but there were no significant changes in other locations. The changes of DPECD, TECA, and CV according to locations are illustrated in Figure 4. Repeat measure ANOVA for DPECD, TECA, and CV showed significant changes in only temporal location. DPECD in postoperative 4 weeks significantly decreased compared to preoperative DPECD (p = 0.010), but there were also no significant DPECD changes in the other locations. TECA and CV in postoperative 1 day and 4 weeks also significantly increased compared to preoperative TECA and CV in only temporal area (TECA: p = 0.012, p = 0.001, CV: p = 0.003, p = 0.001 respectively, repeat measure ANOVA), but there were no significant TECA and CV differences in other locations. The ECD and endothelial cell area were changed significantly in only temporal location irrespective of laterality (Table 2).

Table 1. Preoperative endothelial cell density and area according to location.

Location (Eyes=24)	ECD (cells/mm^2) (Mean±SD)	DPECD (%) (Mean±SD)	Cell area (μm^2) (Mean±SD)	Comparison with central ECD (%)
Center	2562 ±518	19.60 ±1.71	406 ±86	100.0
Superior	2628 ±462	20.54 ±1.52	392 ±77	102.6
Inferior	2421 ±500	19.28 ±1.96	431 ±98	94.5
Temporal	2620 ±382	20.22 ±1.50	389 ±56	102.3
Nasal	2623 ±525	20.34 ±2.21	397 ±90	102.4
P-value†	**0.642**	**0.086**	**0.659**	

ECD = Endothelial cell density

†One way ANOVA

Table 2. The change of endothelial cell density and average cell area according to laterality.

Eyes = 24		Preop. (Mean±SD)	Postop. 4 weeks (Mean±SD)	P-value†		Preop. (Mean±SD)	Postop. 4 weeks (Mean±SD)	P-value†
Center	**ECD (Right eye)**	2673±401	2412±694	0.234	**ECD (Left)**	2492±595	2313±418	0.200
Superior		2859±71	2838±178	0.911		2483±549	2516±499	0.727
Inferior		2527±500	2403±374	0.451		2354±521	2311±485	0.691
Temporal		2776±300	2422±274	**0.004**		2522±412	2246±362	**0.003**
Nasal		2984±158	2709±216	0.119		2397±553	2413±498	0.870
Center	**Cell area (Left eye)**	381±59	442±125	0.187	**Cell area (Left)**	421±100	444±75	0.324
Superior		349±28	358±58	0.741		419±89	412±91	0.739
Inferior		412±109	424±68	0.709		442±96	450±99	0.678
Temporal		363±40	417±49	**0.003**		405±60	456±85	**0.003**
Nasal		335±18	371±30	0.059		436±96	429±88	0.748

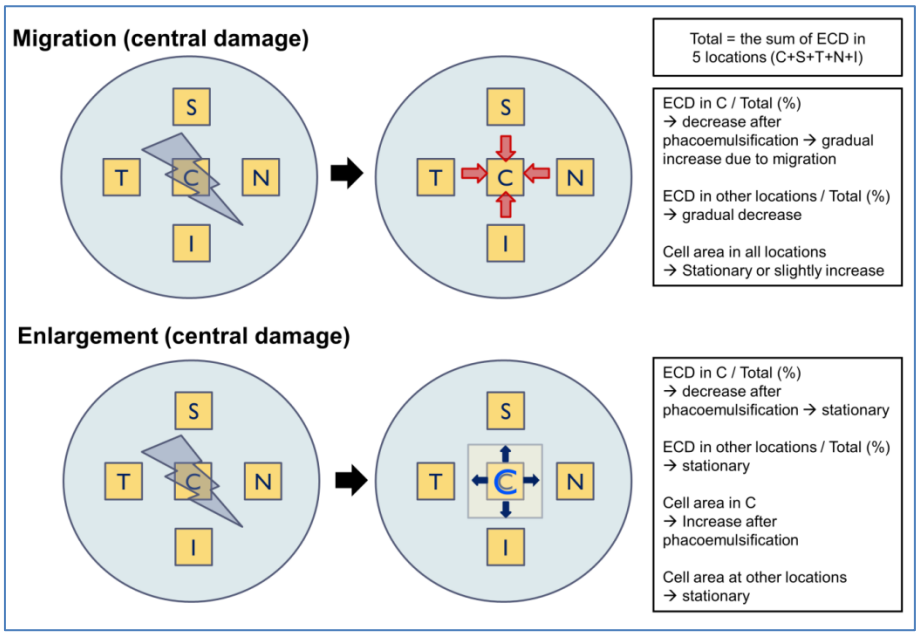
ECD = Endothelial cell density

Preop. = preoperative

Postop. = postoperative

† Paired t-test

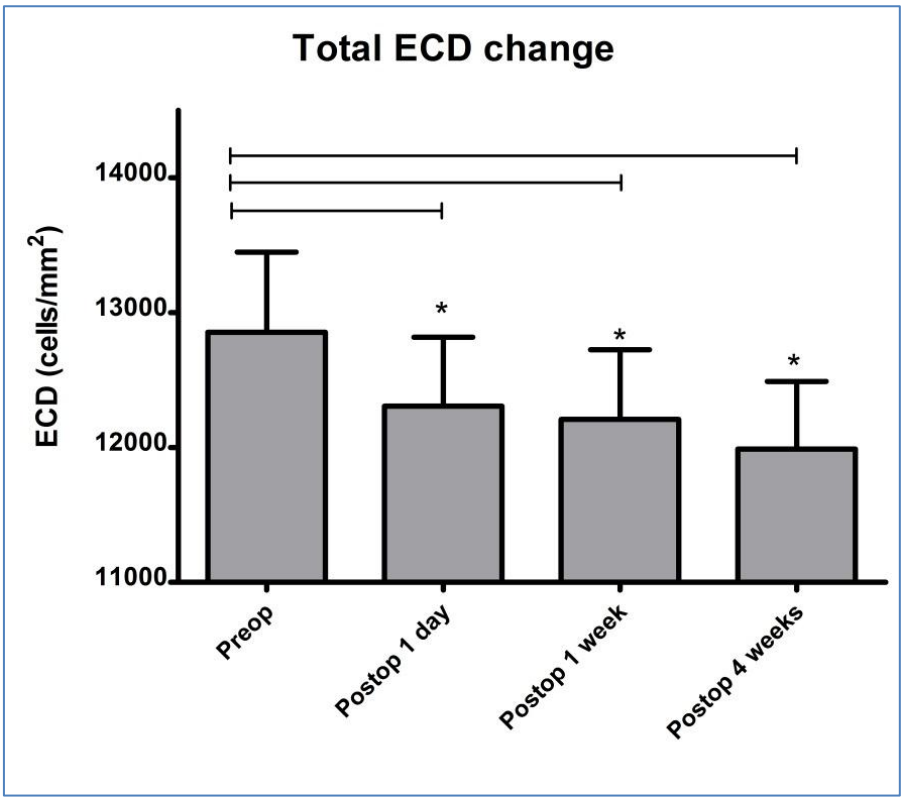
Figure 1. The hypothesis about the corneal endothelial cell recovery mechanism following phacoemulsification (In the assumption of central endothelial damage): cellular migration or enlargement.



ECD = endothelial cell density

C = central location; S = superior paracentral location; I = inferior paracentral location; N = nasal paracentral location; T = temporal paracentral locaion

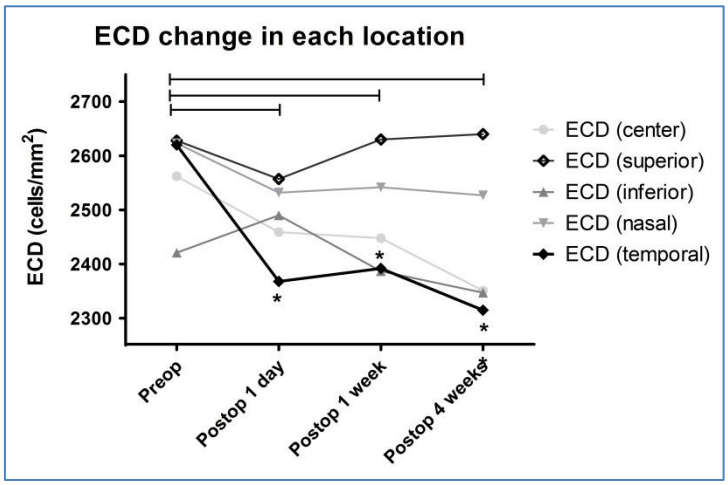
Figure 2. The change of the sum total of endothelial cell densities in central and 4 paracentral(superior, inferior, nasal, and temporal) locations before and after surgery



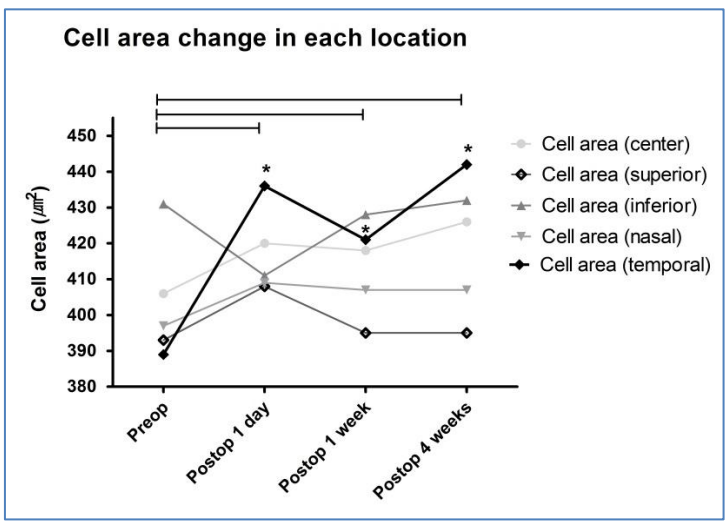
*: Statistically significant (repeat measure ANOVA)

Figure 3. The changes of endothelial cell density (A) and average endothelial cell area (B) according to location in preoperative and postoperative period. Significant changes were only observed at the temporal location.

(A)



(B)



*: Statistically significant (repeat measure ANOVA)

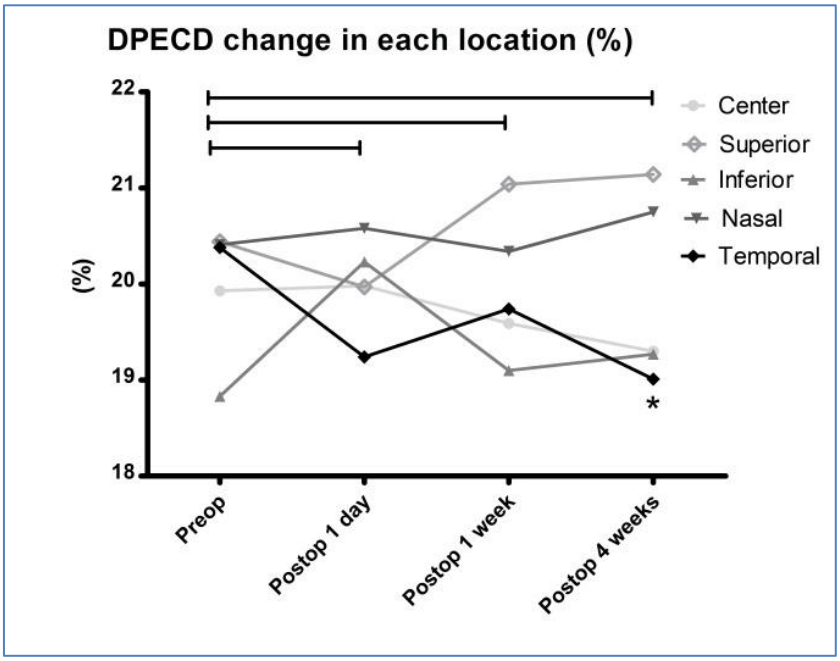
ECD = Endothelial cell density

Preop = preoperative

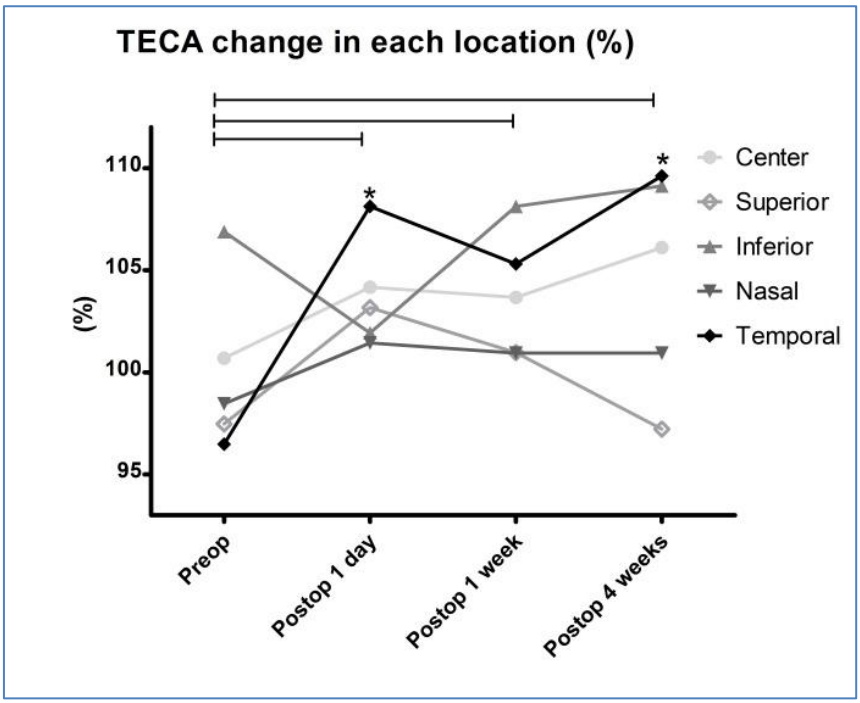
Postop = postoperative

Figure 4. The changes of divisional proportional endothelial cell density(DPECD) (A), the transition of endothelial cell area relative to preoperative average cell area (TECA) (B), and coefficient of variation (CV) (C) according to the location in preoperative and postoperative period. Significant changes were only observed at the temporal location.

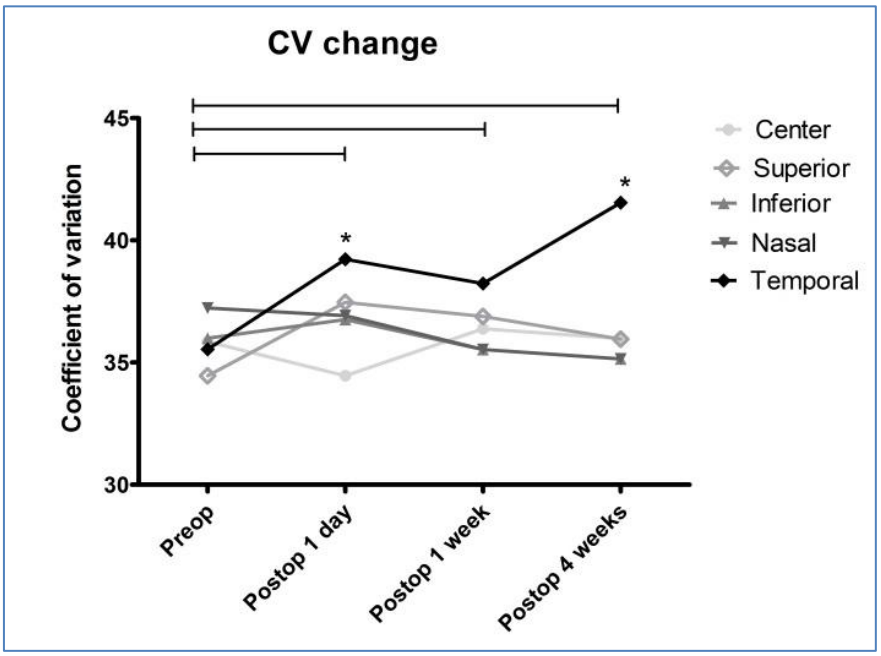
(A)



(B)


TECA change in each location (%)
110
105
100
95
(%)
*
*
Center
Superior
Inferior
Nasal
Temporal
Preop
Postop 1 day
Postop 1 week
Postop 4 weeks

(C)


CV change
45
40
35
30
Coefficient of variation
*
*
Center
Superior
Inferior
Nasal
Temporal
Preop
Postop 1 day
Postop 1 week
Postop 4 weeks

*: Statistically significant (repeat measure ANOVA)

ECD = Endothelial cell density

Preop = preoperative

Postop = postoperative

DISCUSSION

This study were designed to know what(cellular migration or enlargement) mainly act on postoperative ECD recovery after phacoemulsification using the analysis of DPECD, TECA and CV changes in central and 4 paracentral corneal locations. Postoperative DPECD decreased and TECA increased only in the temporal area, compared to preoperative values. CV also only increased in the temporal area. There were no significant changes in other locations. These results well coincided with our hypothesis about enlargement and may indicate that a cellular enlargement is a main mechanism of early endothelial recovery after phacoemulsification.

Once the endothelial single layer has formed, the endothelial cells do not normally replicate in vivo at a rate sufficient to replace dead or injured cells.[19] This relative lack of cell division results in a gradual decrease in endothelial cell density throughout life with an average cell loss.[19] Several studies reported endothelial cell damage after cataract extraction.[4,14,20-29] It has been thought that endothelial damages following phacoemulsification in humans would be recovered by migration or enlargement, but it is not certain which is

the main mechanism of endothelial recovery. To our knowledge, there is no study to investigate the main endothelial recovery pattern after phacoemulsification in human. A lot of results from animal in vivo study, human in vitro study seem to make people have thought that cellular migration and enlargement are taken for granted as recovery patterns after phacoemulsification in human.[6-17] This study can be a fresh attempt for revealing the mechanism of endothelial recovery following phacoemulsification as human in vivo study.

Our results showed no significant ECD difference between central and 4 paracentral locations preoperatively. Previous study showed that the human cornea has an increased ECD in the paracentral and peripheral regions of cornea compared with the central region.[30-32] Because the subjects in our study(68.1 ± 10.0 years) are older than prior study(mean age: 29.3 ± 7.1 years), which may explain this disparity in the endothelial cell distribution. Additional studies evaluating the endothelial distribution are needed.

Our study showed that only temporal paracentral endothelial cell significantly decreased and enlarged after phacoemulsification using temporal

corneal incision, contrary to expecting that central endothelial cell damage would happen mainly. Those seems to be related with endothelial wound by main clear corneal incision, the phaco-tip movement. Interestingly, the side incision does not appear to be greatly affected the endothelial damage at the adjacent superior and inferior paracentral locations, irrespectively of laterality. Previous studies showed wider main corneal incision was related with larger postoperative endothelial cell loss in cataract surgery.[21,33] The incision wider than specific length seems to induce endothelial damage of adjacent area. This study showed no statistically significant postoperative ECD decrease in central location. Enrolled patients were diagnosed primarily with moderate cataracts, and the mean CDE value was relatively low compared to previous torsional phacoemulsification studies.[1,3,29,34,35] It appears to be a cause of minimal endothelial damage in central location. If more patients were enrolled in the study, it might have resulted in a significant decrease of central ECD. Instead, the sum total of ECD in 5 locations were significantly decreased postoperatively and this is similar with endothelial changes following phacoemulsification in several studies.[3,4,8,20,22,27,33,36-38]

Recently, a renewal zone, in the periphery of the human corneal endothelium, where endothelial cells divided very slowly and migrated toward the center but probably showed fragility were introduced.[39] The study suggested the existence of endothelial stem cells or transient amplifying cells similar to limbal epithelial stem cells. On the basis of this finding, our results may reflect damage to corneal endothelial stem cells caused by primary temporal corneal incision and repetitive phaco tip movement, which may consequently hinder endothelial migration temporally. Furthermore, a disparity in endothelial stem cell activity according to patient age may explain the lack of significant difference in preoperative ECD between 5 locations.

There are several notable limitations of the present study. The sample size was small, and the follow-up period was short. Our results may be limited in the moderate cataract and phaco-chop technique surgery. Intraobserver variability also could affect the results. However, variability was maximally controlled by using a same machine and by a single experienced surgeon and examiner. Because the estimate for the repeatability of specular microscopy was reported about ±8.2%[40], and temporal ECD change in our study

exceeded this range (data not shown), the postoperative ECD change in this study does not appear to be the results of the intraobserver variability. All patients' data had a normal distribution, which also ensured that postoperative ECD changes were meaningful. The majority of endothelial repair occurs within 1 month after cataract surgery;[41] therefore, the short follow up period is unlikely to be a critical limitation. The method to analyze central and paracentral DPECD, TECA, and CV postoperatively is a creative and simple approach for evaluating the main mechanism of endothelial recovery following phacoemulsification and may be applied to various intraocular and corneal surgeries. Measurement of further peripheral ECD may allow more precise analysis of endothelial cell changes after surgery.

In conclusion, the postoperative change of ECD, cell area, DPECD, TECA, and CV after phacoemulsification is limited to the temporal area adjacent to the main corneal incision; These results reveal that cellular enlargement may be the main mechanism of early endothelial cell recovery after phacoemulsification.

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초 록

목적: 백내장 수술 후 초기 각막 내피세포의 주요 회복 기전이 세포 이동인지 아니면 세포의 확장인지를 알아보고자 한다.

방법: 분당 서울대학교 병원에서 중등도의 백내장으로 진단받고, 2.75mm 의 이측 투명각막절개를 이용한 성공적인 초음파유화술을 받은 50-80 세 사이의 24 명의 환자들을 대상으로 전향적 관찰 연구가 수행되었다. 비접촉 경면현미경을 통해, 중심부 및 주변부 4 구획 (상측, 하측, 이측, 비측)의 각막 내피세포 밀도(ECD)와 내피세포 면적이 계산되었다. 각 구획에서의 내피세포 밀도, 크기, 5 구획의 총 내피세포 총합 대비 각 구획 내피세포의 분율(DPECD), 술 전 평균 내피세포 면적 대비 각 구획 내피세포 면적의 변화 (TECA), 변이 계수 (CV)가 술 전, 술 후 1 일, 1 주, 4 주째 조사되었다.

결과: 이측부에서만 술 후 1 일, 1 주, 4 주 째 내피세포의 밀도는 유의하게 감소하였고 (각각 $p = 0.010, 0.015, 0.003$), 세포 면적은 유의하게 증가하였다. (각각 $p = 0.008, 0.013, 0.002$) 술 후 DPECD 도 술전에 비해 오직 이측부에서만 유의하게 감소하였고, TECA 와 CV 도 이측부에서만 유의하게 증가하였다. 다른

구획에서는 술 전과 술 후 내피세포 밀도, 세포 면적, DPECD, TECA, CV 는 유의한 차이를 보이지 않았다.

결론: 술 후 내피세포 밀도, 세포 면적, DPECD, TECA, CV 의 유의한 변화는 각막절개창에 인접해 있는 이측부에서만 발생하였다. 각막 내피세포의 이동보다는 확장이 수정체 유화술 후 초기 내피세포 회복의 주요 기전일 것으로 생각된다.

주요어: 수정체유화술, 각막 내피세포, 세포 이동, 세포 확장, 내피세포 회복 기전

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