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석사학위 논문

Clinical outcomes of Epi-LASIK

- 1-Year-Long Results of Flap ON/OFF
with Mitomycin-C ON/OFF -

조선대학교 대학원

의 학 과

김 성 택

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에피라식에서 각막상피편 보존 여부와 마이토마이신
사용유무가 1년 내 임상적 결과에 미치는 영향 비교

2010년 2월 25일

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이 논문을 의학 석사 학위신청 논문으로 제출함

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에피라식에서 각막상피편 보존 여부와 마이토마이신
사용유무가 1년 내 임상적 결과에 미치는 영향 비교

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목적 : 에피라식에서 각막상피편 보존 여부와 마이토마이신 사용유무에 따라 각막혼탁과 통증 정도, 만족도 등 임상적 결과를 평가하고 비교하였다.

방법 : 무작위화 하지 않은 후향적인 비교연구로써 -1.5D에서 -8.0D 사이의 근시가 있어 에피라식수술을 받은 198명 394안을 대상으로 하였다. 환자는 각막상피편 보존 여부와 마이토마이신 사용 유무에 따라 4가지 군으로 분류하였다. 수술 1일, 1개월, 3개월, 6개월, 1년 후에 각 군간의 비교를 시행하였다.

결과 : 수술후 1일째 평균나안시력은 Off-flap군이 On-flap군에 비해 통계학적으로 유의하게 좋았다($P = 0.002$). 수술 1년후 구면계수치는 모든 군간에 통계학적으로 유의한 차이가 없었다($P = 0.305$). 술후 통증 정도는 off-flap군에서 유의하게 낮았고($P = 0.010$), 수술 만족도 또한 off-flap군에서 더 높았으나 통계학적으로 유의한 차이는 보이지 않았다($P = 0.248$).

결론 : 에피라식을 이용한 근시 교정술은 각막상피편 보존 여부나

마이토마이신 사용 유무에 관련 없이 모두 안정적인 결과를 나타냈다.
마이토마이신을 사용하는 경우 기대했던 효과는 나타나지 않았다.
결론적으로는 각막상피편을 보존하지 않는 것이 보존하는 방법에 비해
시력회복이 빠르고 술후 통증이 적었다.

Introduction

Since the introduction of PRK (photorefractive keratectomy) by Trokel in 1983, aggressive research has been carried out on safer and more effective surgical methods.¹ LASIK (laser in situ keratomileusis) was developed as an improved method for reducing pain, corneal haziness and regression to myopia following PRK.² However, LASIK also resulted in some complications such as irregular flap, flap striae, epithelial ingrowth and corneal ectasia that could develop after deep ablations. This led to further research on safe surgical methods.³ LASEK (Laser epithelial keratomileusis), first suggested by Massimo Camellin in 1999, is a method that incorporates the advantages of both PRK and LASIK.⁴ LASEK still has some disadvantages, however, because it involves the use of alcohol in flap formation. Hence, in 2002, Pallikaris developed epi-LASIK, a method using epikeratome instead of alcohol.⁵ As an alternative surface ablation procedure, epi-LASIK leads to more stable vision correction, avoids the toxicity of alcohol and can completely remove the corneal epithelium from the basement membrane (in contrast to LASEK).⁶ There are some published studies on epi-LASIK, but their validity is questionable because of the low number of cases studied and short follow-up duration.⁶

The epi-LASIK procedure comprises two types: on-flap and off-flap. These classifications describe whether the epithelial flap is preserved during the operation. This distinction is important because the preservation or non-preservation of the flap can affect the clinical results, postoperative pain and satisfaction degree of the patient. Mitomycin-C (MMC) is an antibiotic derived from *Streptomyces caespitosus*. Although MMC was originally used as a systemic chemotherapeutic agent, topical MMC has been widely used in ophthalmic indications. In recent years, MMC has

gained popularity for use with glaucoma filtering surgery to prevent scarring and resultant bleb failure, and as an adjunctive treatment in pterygium surgery.⁷⁻⁹ Recently, MMC has been advocated as a potential modulator of wound healing after refractive surgery.^{10, 11} There have been few reports on off-flap epi-LASIK; furthermore, in an initial investigation, Wang et al. noted some limitations (e.g., low number of cases and short study duration).¹² A comparative study of MMC use and non-use has been carried out, but, to our knowledge, there is no research examining the combination of flap (on or off) and MMC dose.¹³ We aimed to evaluate clinical outcomes, corneal haziness, pain scores and satisfaction scores after the epi-LASIK procedure performed either on-flap or off-flap with or without 0.02% MMC treatment.

Methods

Patient Population

We retrospectively reviewed the charts of 198 patients (394 eyes) who underwent epi-LASIK surgery performed by a single surgeon between October 2005 and February 2007. Written informed consent was obtained from all patients before the operation. Enrolled patients fulfilled the criteria for inclusion in the study: age of at least 18 years; spherical equivalent between -1.5D and -8.0D; no ocular disease (e.g., corneal dystrophy); no previous refractive surgery or systemic disease likely to affect epithelial healing. All patients had a minimum of 12 months of follow-up after surgery. Preoperative examinations included: assessment of clinical manifestations and history taking; measurement of UCVA (uncorrected visual acuity), BCVA (best corrected visual acuity), refractive errors, cycloplegic refractions and intraocular pressure; pachymetry; corneal topography; specular microscopy; measurement of scotopic pupil size; slit-lamp biomicroscopic examination; dilated fundus examination.

Surgical Procedure

After the application of topical anaesthesia with 0.5% proparacaine hydrochloride (Alcane®, Alcon, USA), we exposed the cornea using an eyelid speculum (Moria, Antony, France). We cleaned the cornea, conjunctiva and conjunctival sac with a balanced salt solution (BSS, Alcon, USA) at 4°C and then separated the corneal epithelium using an Epikeratome (Moria, Antony, France). Off-flap refers to the condition without replacement of the epithelium segment directly after surgery, whereas on-flap refers to the condition with replacement. We removed the entire corneal epithelial flap carefully such that no residual epithelium remained by using dry Merocel (Weck-cel®, Medtronic Xomed Inc., USA)

in the off-flap groups. The cornea was ablated with an Excimer laser (VISX Star S4, USA). The application of a sponge (7 mm diameter) soaked with 0.02% MMC was separately recorded; in cases wherein the soaked sponge was used, it was placed on the ablated stroma for 2 minutes and then removed. The corneal surface and the entire conjunctival fornix were irrigated with BSS (50 mL) kept at 4°C to reduce postoperative pain and remove any residual MMC. The flap in on-flap groups was repositioned carefully so as not to tear the flap with the needle used for irrigation. After surgery, we recommended to patients a period of approximately 2 minutes to allow the eyes to dry, followed by wearing of therapeutic contact lenses (Acuvue Oasys®, Johnson & Johnson, USA). The patients were then examined with slit-lamp biomicroscopy. The patients were given 0.5% moxifloxacin eyedrops (Vigamox®, Alcon, USA) four times per day for the first postoperative week and 0.1% diclofenac sodium (Voltaren®, SDU, Novartis, USA) twice per day for the first postoperative 3 days. After confirming the repair of the corneal epithelium, the contact lenses were removed. We recommended the application of 1% prednisolone acetate (Pred Forte®, Allergan, USA) four times per day for the first week as well as 0.1% corticosteroids (Flumetholone®; Santen, Osaka, Japan) four times per day for the first week. These medications were tapered from 4 times per day to once per day at intervals of 1 week for 4 weeks. Patients were also given preservative-free 0.5% carboxymethylcellulose (Refresh plus®, Allergan, USA) for artificial tears six times per day for the maintenance of tear film and regular ocular surface. We performed daily follow-up for these patients until recovery of the corneal epithelium was complete.

Follow-up

After removal of the therapeutic contact lens, patients were followed up

on day 1 as well as at 1-, 3-, 6- and 12-month postoperative intervals. Postoperative examinations included measurement of UCVA, BCVA and refractive error; biomicroscopy; applanation tonometry; corneal topography. Corneal haze formation was subjectively evaluated by a single ophthalmologist at 1 year after surgery using the system reported by Fantes et al.¹⁴: 0, completely clear; 1, prominent haze not interfering with the visibility of fine iris details; 2, mild obscuration of iris details; 3, moderate obscuration of the iris and lens; 4, complete opacification of the stroma in the area of the ablation. Pain scores with the removal of therapeutic contact lenses were included in the subjective evaluation forms completed by patients; pain scores were evaluated according to the Numerical Pain Intensity Scale (0, no pain to 10, worst possible pain). The questionnaires were collected during the visit only on the second postoperative day, because it has been suggested that there are no significant differences in pain during the entire period of epithelial healing. Satisfaction scores at 1 year after surgery were also included in the subjective evaluation forms; these scores were evaluated according to a predetermined scale ranging from 0 (extremely regret surgery) to 10 (perfectly satisfied with surgery). In the retrospective study, we classified the patients with a follow-up over 12 months after surgery according to the on-flap or off-flap method and treatment with or without 0.02% MMC. Thus, the following four groups were formed: Group I, on-flap without MMC, 181 eyes; Group II, on-flap with MMC, 52 eyes; Group III, off-flap without MMC, 93 eyes; Group IV, off-flap with MMC, 68 eyes. Patients were not informed of their group membership.

Statistical Analysis

To increase the reliability of the data, all experiments were repeated three times; the average values were obtained. SPSS for Windows,

Version 11.5 (SPSS Inc., Chicago, USA) was used to compute routine statistics. The data were analysed for significance by a repeated-measures ANOVA followed by Duncan's multiple range tests for post hoc comparison. The data are expressed as a mean percentage of the control value plus S.E.M. (structural equation modelling). A p-value of <0.05 was considered statistically significant.

Results

We evaluated 394 eyes of 198 patients (63 eyes of 32 males and 331 eyes of 166 females). The mean age of the subjects was 29.69 ± 5.02 years. Patient ages showed the following distribution: 48 eyes (20s), 9 eyes (30s) and 6 eyes (40s) in males; 236 eyes (20s), 85 eyes (30s) and 10 eyes (40s) in females. The mean spherical equivalents of the subjects were -5.77 ± 1.52 D (I), -6.43 ± 1.39 D (II), -6.22 ± 1.62 D (III) and -6.27 ± 1.30 D (IV) before surgery. The mean central corneal thicknesses were 481.10 ± 24.04 μm , 485.15 ± 16.28 μm , 488.41 ± 32.12 μm and 488.44 ± 19.44 μm . The mean corneal curvature (K) values were 44.06 ± 1.27 D, 43.85 ± 1.09 D, 43.69 ± 1.80 D and 43.89 ± 1.58 D. There was no statistically significant difference between the four groups ($P=0.131$, $P=0.525$) (Table 1). The UCVA at post-operative day 1 in the off-flap groups (Group III, IV) was significantly better than in the on-flap group (Group I, II) ($P=0.002$), regardless of whether or not MMC was used. Therefore, fast recovery of UCVA was notable for the off-flap group. However, changes in UCVA for any of the groups were not statistically significant at month 1, 3, 6 or 12 (Figure 1). After one year, mean spherical equivalents were as follows: Group I: -0.48 D (± 0.49), Group II: -0.48 D (± 0.73), Group III: -0.45 D (± 0.38), and Group IV: -0.26 D (± 0.56). Refraction was stabilised in all groups, and there was no significant difference between the groups ($P=0.305$; Figure 2). There was no statistically significant change in keratometry at any time ($P=0.128$; Figure 3). We noted opacity (Grade I in eight eyes and Grade II in two eyes); however, there was no opacity greater than Grade II. The opacity grade was not affected by on- or off-flap methods or by MMC use ($P=0.533$; Figure 4). We established the grade of pain from 0 (no pain) to 10 (worst possible pain). According to patient self-reports, pain was significantly higher in the on-flap groups (Groups I, II) (3.50 ± 1.14) than the off-flap groups (Groups III, IV) (2.77 ± 1.06) ($P=0.010$). The grade of patient satisfaction was assessed by self-report methods (from 0 to

10) and showed that satisfaction was higher in the off-flap groups (Groups III, IV) (9.87 ± 0.68) than the on-flap groups (Groups I, II) (9.61 ± 0.71). However, there was no statistically significant difference between any of the groups ($P=0.248$; Figure 5).

Discussion

Over the past few years, there has been an emerging tendency toward performance of surface ablation procedures. Epi-LASIK is a new approach to LASIK that uses a prototype device to achieve epithelial separation mechanically. Pallikaris et al.⁶ invented the Epikeratome as an alternative surface ablation procedure in 2002, and demonstrated that epi-LASIK produces better stabilised visual correction than LASEK in patients with myopia. Furthermore, various studies reported that the corneal epithelium was rarely damaged when separated mechanically and completely separated from the basement membrane; in contrast, when separated by alcohol, the corneal epithelium was greatly damaged and separated from the intra-basement membrane.⁵ LASIK uses the microkeratome, an epikeratome instrument made of PMMA that is also used in the epi-LASIK procedure, for surface ablation. Because the blade of the epikeratome is more blunt than that of the microkeratome, the basement membrane of the corneal epithelium is not damaged. The epikeratome can thus separate the cell layer of the corneal epithelium as a thin plate structure. Hence, Pallikaris et al.⁵ reported that this device could reduce pain and corneal scarring. There have been several reports that epi-LASIK induces less early postoperative pain than PRK¹⁵⁻¹⁷. Subsequently, epi-LASIK has been widely used as a surgical method for the correction of myopia. The procedure can be divided into on-flap and off-flap methods according to whether the flap is preserved or not during epi-LASIK surgery. Off-flap epi-LASIK, as a modified surface ablation, completely removes the epithelial flap after laser ablation. Following flap removal from the corneal epithelium, there can be pain during the re-epithelialisation period. On-flap requires the repositioning of the epithelial flap, which is thought to act as a natural contact lens that

diminishes inflammation and post-operative pain, and decreases the formation of opacity. Unexpectedly, however, off-flap epi-LASIK resulted in significantly less pain in our study than on-flap epi-LASIK. Furthermore, good clinical outcomes occurred after the off-flap epi-LASIK procedure. It is possible that the off-flap epi-LASIK patients experienced less inflammation and faster recovery because the epithelial margin was cut clearly and application of cool BSS reduced the pain. Wang et al.¹² found no significant difference in postoperative pain levels between the two groups. The subjects in this study had moderate myopia. Their refractive errors were in the range of $-1.5D \sim -8.0D$. There was no significant difference in the change of UCVA or spherical equivalent among the groups at one postoperative month. This result was similar to the outcome of O'Doherty et al., who found no difference in recovery of the UCVA and spherical equivalent at three months after surgery¹⁸. According to Wang et al.¹², off-flap epi-LASIK offers comparable visual and refractive outcomes to on-flap epi-LASIK along with rapid recovery in the early post-operative period. This study also showed that UCVA was better in the off-flap group on post-operative day 1. According to Wang et al.¹², off-flap epi-LASIK resulted in lower levels of haze than on-flap epi-LASIK. In our study, however, corneal haziness was independent of the on- or off-flap procedure. Recently, MMC has been successfully used for the treatment and prevention of corneal haze after surface excimer laser ablation. It binds and cross-links the DNA in the nuclei, primarily affecting rapidly proliferating cells.¹⁹ MMC limits the proliferation of activated keratocytes and induces keratocyte apoptosis in the anterior stroma.²⁰ These features account for its ability to prevent or treat haziness. Camellin²¹ studied the effects of prophylactic MMC (0.01%) in eyes that received LASEK treatment for myopia. MMC effectively inhibited haze development in comparison to control eyes with high

myopia. However, Camellin noted potential side effects (e.g., a decrease in BCVA, prolonged epithelial recovery time and over-correction). In contrast, de Benito-Llopis et al.²² found that LASEK procedures with MMC seemed to yield stable refractive results. Thus, it has been suggested that MMC be used to prevent haze formation in moderate myopia. In our study, however, corneal haziness was independent of the on-flap or off-flap procedure used as well as MMC use. MMC obviously reduces haze, although the optimal concentration and application time for MMC are debatable. The reported time varied from 12 seconds to 2 minutes; it is generally accepted that 0.02% MMC is safe and has no epithelial cytotoxic effects.²³ In this study, 0.02% MMC was applied over the ablated stroma for 2 minutes and then removed completely by cool BSS. The myopic correction by epi-LASIK showed stable visual results (as assessed by clinical outcomes) for one year after surgery regardless of the on- or off-flap procedure used and use of MMC. Haziness levels revealed that 0.02% MMC application was less effective than expected. However, we conclude that the off-flap method offers faster visual recovery and less postoperative pain than the on-flap method. Further investigations with a larger number of subjects and longer follow-up periods are warranted.

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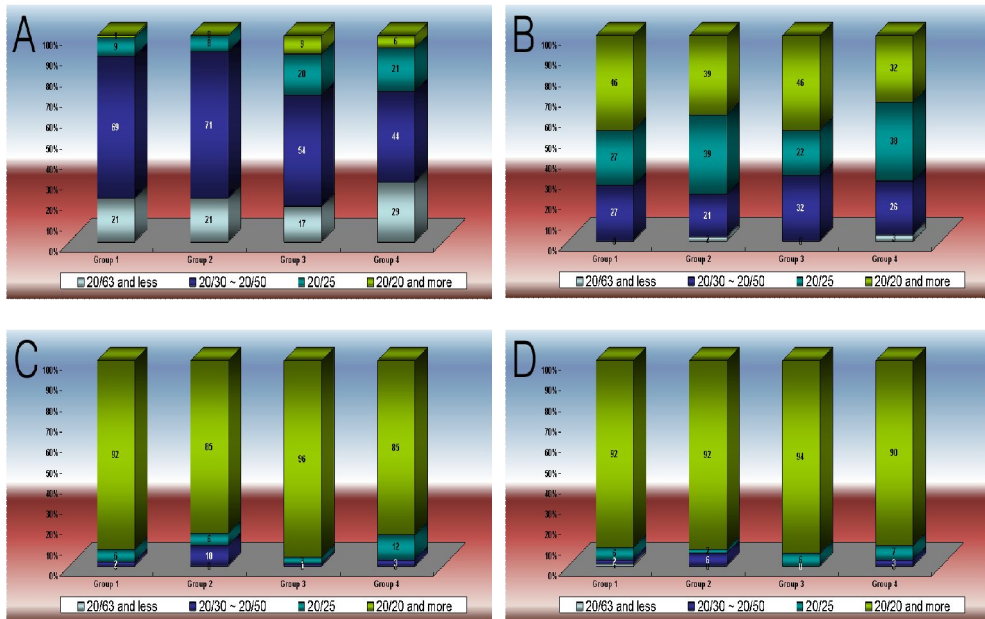
Table 1. Baseline characteristics of eyes for epi-LASIK* surgery

Characteristics	Group I (181)	Group II (52)	Group III (93)	Group IV (68)	p-value
Age, mean (years)±SD [†]	29.48±5.43	30.05±4.03	30.43±5.21	29.28±4.23	0.401
Gender (male/female)	20/161	18/34	19/74	6/62	
Pachymetry, mean (μm)±SD	481.10±24.04	485.15±16.28	488.41±32.12	488.44±19.44	0.131
Preoperative SE [§] , mean (D#)±SD	-5.77±1.52	-6.43±1.39	-6.22±1.62	-6.27±1.30	0.068
Preoperative UCVA [*] , mean±SD	0.14±0.10	0.08±0.11	0.09±0.13	0.10±0.19	0.274
Preoperative BCVA [¶] , mean±SD	1.00±0.12	0.97±0.41	0.98±0.21	0.98±0.11	0.651
Keratometry, mean (D)±SD	44.06±1.27	43.85±1.09	43.69±1.80	43.89±1.58	0.525
Amount of ablation, mean (μm)±SD	87.30±19.80	89.71±14.02	88.87±23.52	85.69±16.14	0.342

*epi-LASIK = epi-laser in-situ keratomileusis; †SD = standard deviation; §SE = spherical equivalent; *UCVA = uncorrected visual acuity, IIBCVA = best corrected visual acuity, #D = diopters

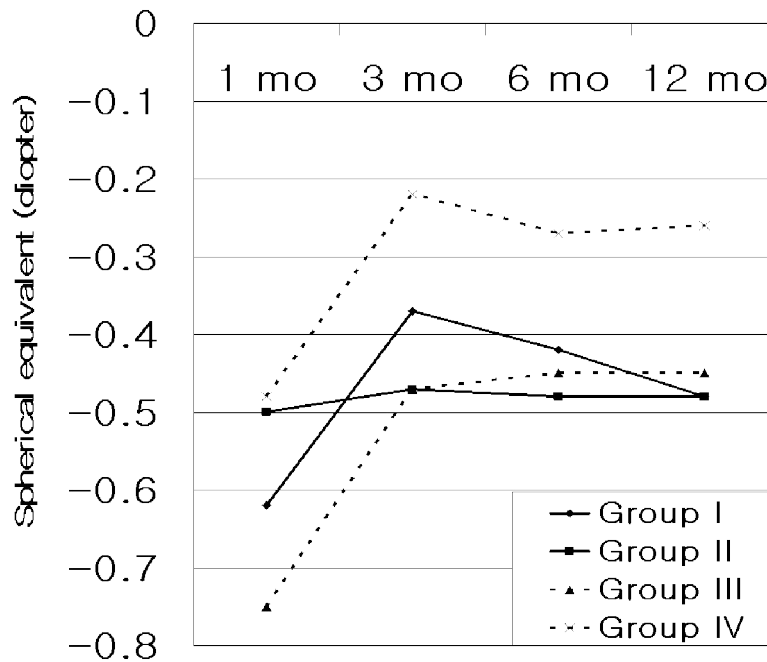
A total of 198 patients (394 eyes) who had undergone an epi-LASIK surgery (63 eyes in 32 males and 331 eyes in 166 females) were reviewed. Patients were classified into four groups: Group I, on-flap without mitomycin C (MMC), 181 eyes; Group II, on-flap with MMC, 52 eyes; Group III, off-flap without MMC, 93 eyes; Group IV, off-flap with MMC, 68 eyes. The mean central corneal thicknesses measured with a pachymeter (pocket type; Biovision, France) showed no statistically significant difference between the four groups ($P = 0.131$). The subjects suffered from mild-to-moderate myopia, with spherical equivalent values ranging from 1.5 D to 8.0 D before surgery. Furthermore, there was no statistically significant difference between the four groups with respect to the preoperative UCVA ($P = 0.274$), BCVA ($P = 0.651$), or mean corneal curvature measured by keratometry ($P = 0.525$).

Figure 1. Mean uncorrected visual acuities (UCVA) following epi-LASIK surgery at different postoperative periods (A, 1 day; B, 1 month; C, 6 months; D, 12 months).



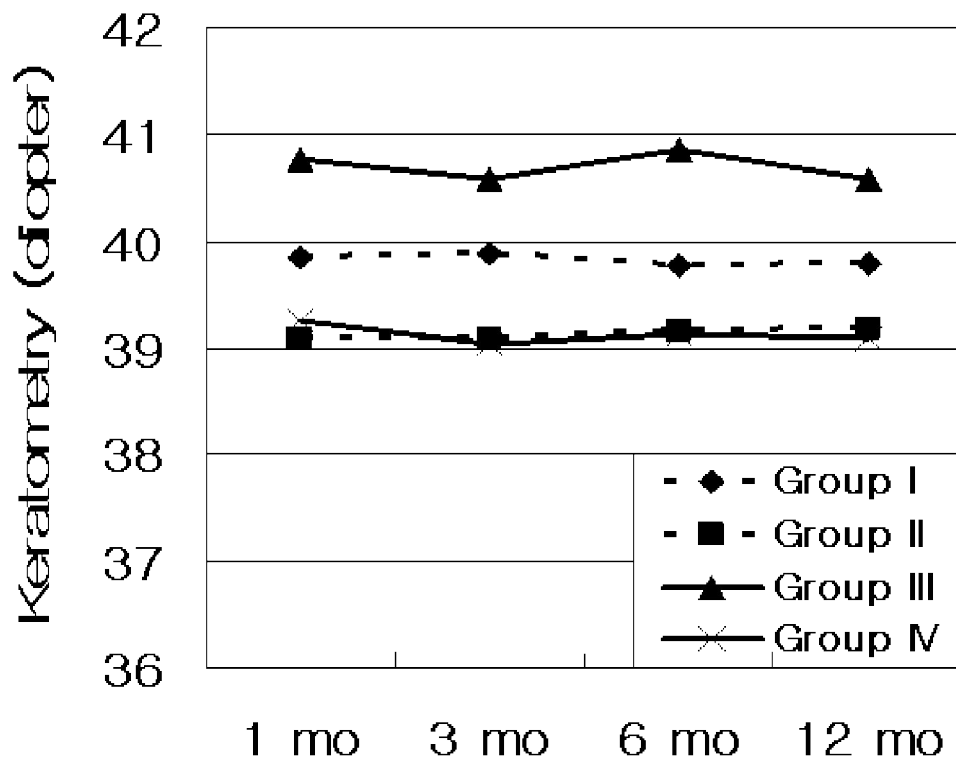
Uncorrected visual acuity (UCVA). The percentages of subjects with UCVA of 20/25 (bluish green) and equal to or greater than 20/20 (light green) at post-operative 1 day (A) were 10% (I), 8% (II), 29% (III), and 27% (IV). Thus, the off-flap groups (Groups III and IV) had significantly better UCVA than the on-flap groups (Groups I and II) ($P = 0.002$). However, changes in UCVA for any of the groups were not statistically significant at 1 month (B), 6 months (C) or 12 months (D) ($P = 0.272$, $P = 0.514$ and $P = 0.643$, respectively).

Figure 2. Mean spherical equivalents following epi-LASIK surgery at different postoperative periods



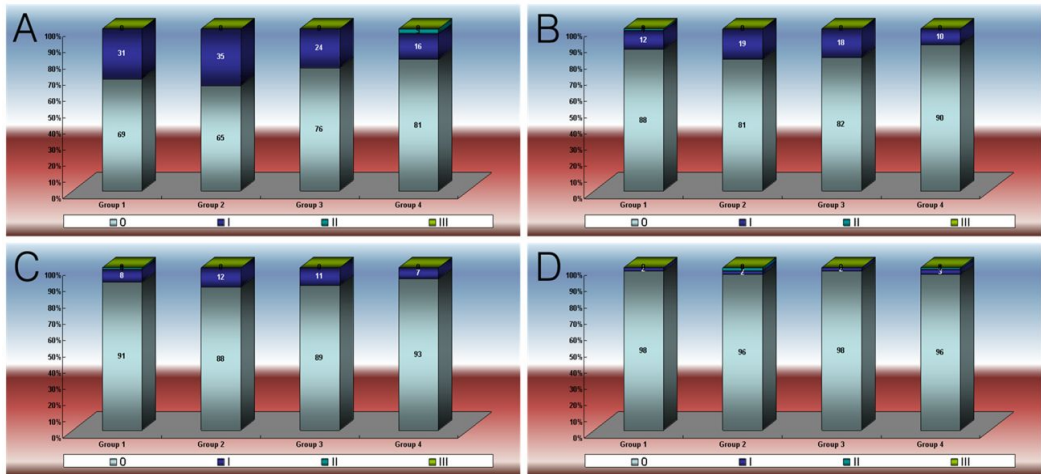
Mild myopia remained until postoperative 1 month; however, the spherical equivalent of myopia was stabilised after 1 month. No significant regression was observed. In the analysis of the mean spherical equivalent correlation, no significant difference was observed ($P = 0.305$).

Figure 3. Keratometry following epi-LASIK surgery at different postoperative periods



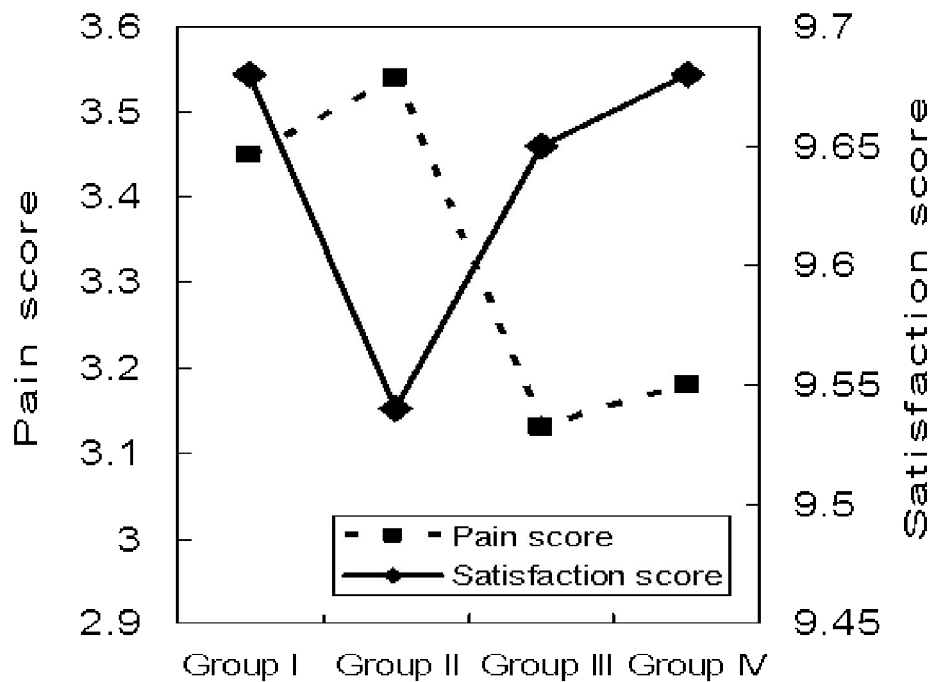
Corneal curvatures were stabilised following surgery. In the analysis of the keratometry correlation, there was no statistically significant change at any time ($P = 0.128$).

Figure 4. Corneal hazes following epi-LASIK surgery at different postoperative periods (A, 1 month; B, 3 months; C, 6 months; D, 12 months).



In the analysis of correlation between the corneal hazes of the four groups subjectively evaluated using this system, the percentages in every opacity grade for all groups did not differ significantly in any period ($P = 0.533$). This finding suggests that the corneal haziness was not affected by the on- or off-flap method used, or by mitomycin C (MMC) use.

Figure 5. Comparison of overall subjective pain and satisfaction scores following epi-LASIK surgery among the four groups



Postoperative pain, subjectively evaluated only on the second postoperative day using the Numeric Pain Intensity Scale (0: no pain ~ 10: worst possible pain), was significantly higher in the on-flap groups (Groups I and II) than the off-flap groups (Groups III and IV) ($P = 0.010$). The grades of postoperative patient satisfaction at 1 year after surgery, which were subjectively evaluated with a predetermined scale ranging from 0 (regret extremely for surgery) to 10 (satisfy perfectly for surgery), yielded similar results in Groups I, III and IV. The scores in Group II were lower than those of the other groups; however, no statistically significant differences were observed between any of the groups ($P = 0.248$).