REVIEW/UPDATE

Duration of topical steroid application after photorefractive keratectomy with mitomycin C

Mojgan Pakbin, MSc, Mehdi Khabazkhoob, PhD, Mohammad Pakravan, MD, Akbar Fotouhi, PhD, Ebrahim Jafarzadehpour, PhD, Mohamadreza Aghamirsalim, MD, Mohammad Amin Seyedian, MD, Hassan Hashemi, MD

Contradictory results of postoperative steroid application in photorefractive keratectomy (PRK) led to a meta-analysis of the existing data to achieve a definite conclusion on the optimum dosage and duration of corticosteroid therapy after PRK. The overall pooled unstandardized mean difference (PUMD) of the corneal haze score was −0.20 (95% CI, −0.29 to −0.12). In subgroup analysis, the PUMD of the corneal haze score was statistically significant in 2 subgroups, −0.57 (−0.85 to −0.30) for 3 to 6 months postoperatively and −0.13 (−0.23 to −0.04) for ≤ 3 months postoperatively. Analysis of the PUMD of postoperative spherical equivalent in participants with low to moderate myopia (≥−6.00 D) and high myopia (<−6.00 D) showed positive effects of steroids on prevention of myopia regression. In conclusion, long-term topical steroid application after PRK seems unnecessary in low and moderate myopia. New randomized clinical trials using current technologies are recommended for postoperative treatments.

J Cataract Refract Surg 2020; 46:622–632 Copyright © 2020 Published by Wolters Kluwer on behalf of ASCRS and ESCRS

Photorefractive keratectomy (PRK), introduced in 1983, was the first refractive surgical technique to be approved by the U.S. Food and Drug Administration in 1996.[1] Although laser in situ keratomileusis (LASIK) became popular, PRK is still preferred by many surgeons because of a lower risk for ectasia, lack of flap complications, and high predictable results.[2] However, subepithelial corneal haze and refractive error regression due to transformation of keratocytes into myofibroblasts are serious complications of PRK.[3,4] Myofibroblasts produce abnormal collagens causing corneal haze, light scattering, and decreased visual acuity.[5,6]

Corneal haze is often associated with myopic regression, and its severity depends on a variety of risk factors.[7] A higher depth of ablation is associated with more corneal haze.[8] In addition, the risk for corneal haze and regression increases with a smaller ablation zone diameter, preoperative astigmatism more than −1.25 diopter (D), and ultraviolet (UV) radiation exposure.[9–12] A brown iris and a history of refractive surgery are other risk factors of corneal haze formation.[9,13]

The corneal inflammatory responses should be minimized by anti-inflammatory agents such as corticosteroids or nonsteroidal anti-inflammatory drugs to prevent corneal haze.[14] Many surgeons believe that corticosteroids can reduce corneal opacity and modulate postoperative myopic regression.[15,16] On the other hand, some studies reject the effectiveness of corticosteroids on corneal haze and consider the role of topical steroids on myopic regression only during their application.[17,18]

Steroids for 3 months postoperatively have been prescribed since the introduction of PRK, but long-term steroid therapy can result in side effects, such as increased intraocular pressure, glaucoma, cataract, delayed epithelial healing, and increased risk for corneal infection.[19,20]

Mitomycin C has been used in refractive surgery since 1997, and its efficacy in inhibiting corneal haze formation and modulating the postoperative corneal healing is confirmed in animal studies.[21–24]

Although corticosteroids are administered routinely after PRK, studies have controversial results and suggestions.

Submitted: July 4, 2019 | Final revision submitted: September 28, 2019 | Accepted: October 28, 2019

From the Noor Ophthalmology Research Center, Noor Eye Hospital (Pakbin), and Translational Ophthalmology Research Center, Tehran University of Medical Sciences (Pakbin), and Department of Psychiatric Nursing and Management, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences (Khabazkhoob), and Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences (Pakravan), and Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences (Fotouhi), and Department of Optometry, School of Rehabilitation Science, Iran University of Medical Sciences (Jafarzadehpour), and Translational Ophthalmology Research Center, Tehran University of Medical Sciences (Aghamirsalim), and Noor Research Center for Ophthalmic Epidemiology, Noor Eye Hospital (Seyedian), and Translational Ophthalmology Research Center, Tehran University of Medical Sciences (Hashemi), and Noor Ophthalmology Research Center, Noor Eye Hospital (Hashemi), Tehran, Iran.

Corresponding author: Hassan Hashemi, MD, Noor Research Center for Ophthalmic Epidemiology, Noor Eye Hospital, Tehran, Italy. Email: hhashemi@noorvision.com.

Published by Wolters Kluwer Health, Inc.

0886-3350/$ - see frontmatter
https://doi.org/10.1097/j.jcrs.0000000000000060

Caubet found that corticosteroids could prevent corneal haze after PRK, whereas O'Brart et al. concluded that steroids had no effect on corneal haze and visual efficiency after PRK, and therefore long-term steroid application is not necessary.[16,18] In a review article, Corbett et al. found no justification for prescribing corticosteroids after PRK, at least for low or moderate myopia.[25] Although topical steroids are routinely used for 3 months after PRK, there is no solid consensus about the dosage and duration of steroid administration. Moreover, it is commonly seen that corneal haze does not develop in some patients who undergo PRK and do not adhere to their 3-month duration of steroid regimen.

Application of mitomycin C and improvements to instrument function with smaller laser spot size have resulted in a smoother corneal surface and less corneal haze. Therefore, long-term corticosteroid application may not be necessary after PRK.

These contradictory results led us to perform a systematic review of the existing data to attain a conclusion about the optimum dosage and duration of corticosteroid therapy after PRK.

METHODS

This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42018102337) available online at: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018102337. All stages of this meta-analysis were performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PICOTS).[26]

Search Strategy

The following databases were searched without any language or location restrictions between January 1, 1980, and February 15, 2019: PubMed, Scopus, Web of Sciences, EMBASE, and Cochrane Library. An extensive search was performed using MeSH (Medical Subject Headings) terms and text words to find the studies related to corticosteroid use in PRK surgery. Figure 1 shows the search strategy prepared for MEDLINE, which was then used in other databases.

Inclusion and Exclusion Criteria

The PICOTS (population, intervention, comparison, outcome, time, study design) criteria were: (1) population: refractive surgery candidates aged 18 years or older who underwent PRK, laser subepithelial keratomileusis, or epi–LASIK without a history of ocular surgery; (2) intervention: eyes treated with corticosteroids; (3) comparison: placebo, nothing, or nonsteroidal anti-inflammatory medicine as postoperative treatment, with or without the use of mitomycin; (4) outcome: corneal haze score and myopic regression; (5) time: January 1, 1980, until January 28, 2018; (6) study design: all studies were included regardless of their design.

Studies conducted in patients with a history of ocular surgery were excluded. Animal or laboratory studies, review articles, letters, editorials, and conference abstracts were also excluded.

Study Selection and Data Extraction

Studies extracted from the databases were entered into EndNote X7 (Clarivate). Duplicates were removed, and then 2 reviewers (M.P., M.K.) screened the studies independently to select studies that met the inclusion criteria in 2 stages: evaluation of studied based on titles and abstracts and evaluation based on full texts. Any disagreements were resolved through discussion or a third reviewer. The following data were extracted: the first author's name, publication year, study location, study design, surgery type, ablation diameter, quality assessment, sample size, steroid duration, group of intervention or control, preoperative spherical equivalent (SE), follow-up time, and outcome. The eligible data were entered into Excel files (Microsoft). The kappa coefficient between the 2 reviewers was 89%. Blinding and task separation was used in the study selection procedure.

Assessment of Study Quality

Quality assessment was performed using the Consolidated Standards of Reporting Trials (CONSORT) checklist for clinical trials and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for observational studies. Each item in these checklists received a score of 1, and the final score was calculated in percent. The results were categorized into 4 groups: very low quality (less than 20%), low quality (20% to 40%), moderate quality (40% to 60%), high quality (60% to 80%), and very high quality (more than 80%). Low-quality studies were excluded from the meta-analysis.[27,28]

1: photorefractive keratectomy [text word] OR photorefractive keratectomy [Mesh term]
2: laser-assisted sub epithelial keratectomy [text word] OR laser-assisted sub epithelial keratectomy [Mesh term]
3: Epi-LASIK [text word] OR Epi-LASIK [Mesh term]
4: 1 OR 2 OR 3
5: Steroid [text word] OR Steroid [Mesh term]
6: Corticosteroid [text word] OR Corticosteroid [Mesh term]
7: Prednisolone [text word] OR Prednisolone [Mesh term]
8: Fluorometholone [text word] OR Fluorometholone [Mesh term]
9: Betamethasone [text word] OR Betamethasone [Mesh term]
10: Dexamethasone [text word] OR Dexamethasone [Mesh term]
11: Loteprednol [text word] OR Loteprednol [Mesh term]
12: 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11
13: Corneal haze [text word] OR Corneal haze [Mesh term]
14: Corneal opacity [text word] OR Corneal opacity [Mesh term]
15: Post-operative haze [text word] OR Post-operative haze [Mesh term]
16: Corneal opacification [text word] OR Corneal opacification [Mesh term]
17: Stromal haze [text word] OR Stromal haze [Mesh term]
18: Subepithelial haze [text word] OR Subepithelial haze [Mesh term]
19: Myopic regression [text word] OR Myopic regression [Mesh term]
20: 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
21: 4 AND 12 AND 20

Figure 1. Search strategy based on PICOTS for MEDLINE (Epi-LASIK = epi–laser in situ keratomileusis; MeSH = Medical Subject Headings).

Outcomes

The outcomes were mean corneal haze score and postoperative mean SE. The postoperative steroid duration was evaluation of the corneal haze score and postoperative SE was performed in 2 categories as follows: (1) steroid duration <3 months (months postoperatively) and (2) steroid duration ≥ 3 months. The time of outcome measurement was classified into 4 groups, including (1) follow-up ≤ 3 months; (2) follow-up > 3 to ≤ 6 months; (3) follow-up > 6 to ≤ 12 months, and (4) follow-up > 12 months. The preoperative SE was evaluated in 2 groups as follows: (1) preoperative SE ≥ −6.00 D and (2) preoperative SE < −6.00 D.

Statistical Methods and Assessment of Heterogeneity

All analyses were performed using STATA, version 14.0. For each study, the sample size and the mean and steroid duration of corneal haze and SE were extracted in the control and intervention groups before refractive surgery and during postoperative follow-ups. The data of corneal haze and SE were extracted from figures in some studies.[29–31]

The mean difference was calculated to determine the difference between groups. Standard error was calculated using the following formulas:

$$\left[s^2_{pooled} = \left(\frac{s_1^2(n_1-1)+s_2^2(n_2-1)}{n_1+\ n_2-2}\right)\right] \qquad \sqrt{s_p^2\left(\frac{1}{n_1}+\frac{1}{n_2}\right)}$$

The Cochran Q test of heterogeneity was used to determine heterogeneity, and its amount was calculated by I^2 statistic. $I^2 > 70\%$ was considered high heterogeneity based on the Higgins classification. A fixed-effect model was used to estimate the pooled mean difference (a random-effect model was used if $I^2 > 70\%$). Because of the similar outcome units in the control and intervention groups, we used the pooled unstandardized mean difference (PUMD) in this meta-analysis. Ultimately, a meta-regression model was applied to evaluate the effect of age, SE, study design, sample size, publication year, study quality, and ablation diameter on heterogeneity between studies for haze and postoperative SE. The significance level was set at .05 in all analyses.

RESULTS

Study Selection

Of 1262 records identified in electronic databases between January 1, 1980, and February 15, 2019, 320 studies were excluded because of duplication. Then, the titles and abstracts of the remaining 942 studies were read, resulting in exclusion of 863 irrelevant records. After reading the full texts of 79 studies, 68 articles were excluded because they did not meet the eligibility criteria for the review. One study was excluded despite having inclusion criteria because it was impossible to calculate the pooled SE.[18] Two other studies were also excluded because of their low quality.[27,28] Eventually, 7 studies were included in meta-analysis. Corneal haze and SE were assessed in 6 and 5 studies, respectively (Figure 2).[29–35]

Study Characteristics

Two studies contained more than 1 study with different designs in each.[29,34] Two studies were published by Baek et al. in 1997. The preoperative SE was referred to as Baek (1997)-1, and the second was referred to as Baek (1997)-2.[29,30] Baek (1997)-1 consisted of 2 studies: Baek

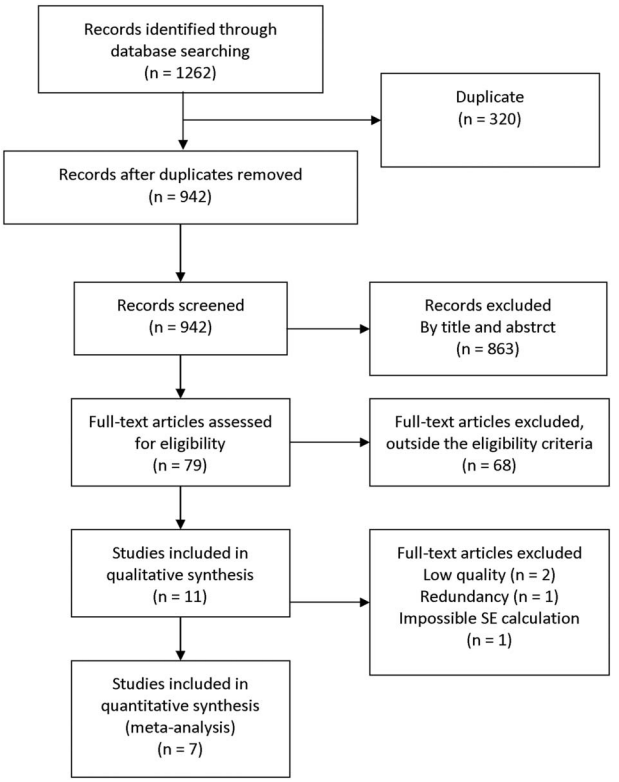

Figure 2. Flowchart of the study selection process.

(1997)- 1(A) and Baek (1997)- 1(B). Baek (1997)-2 had 2 control groups referred to as Baek (1997)-2 (Crt_1) and Baek (1997)-2 (Crt_2). In 1994, Fagerholm et al. published a study consisting of 3 studies: Fagerholm (1994); (A), Fagerholm (1994); (B), and Fagerholm (1994); (C).[34] Fagerholm (1994); (C) had 2 intervention groups: Fagerholm (1994); C (Int_1) and Fagerholm (1994); C (Int_2) in which steroids were prescribed for 5 weeks and 3 months, respectively.

Supplemental Table 1 (see Supplemental Digital Content, http://links.lww.com/JRS/A30) shows the details of the studies. Six of the 7 studies (Aras et al., Badala et al., Baek (1997)- 1(A), Baek (1997)- 2, Gambato et al., and Gartry et al.) had an RCT design, and 4 (Baek (1997)- 1(B), Fagerholm (1994); (A), Fagerholm (1994); (B), and Fagerholm (1994) (C)); had a historical cohort design.[29,30,32–35]

The maximum (2.33) and minimum (0) corneal haze scores were reported in control groups 4 and 12 months postoperatively, respectively.[30,35] The maximum (+2.39 D) and the minimum postoperative SEs (−3.00 D) were reported in control groups 3 weeks and 6 months postoperatively, respectively.[30,33]

Corneal Haze Score

The corneal haze score was graded from 0 to 4 in studies, with 0 indicating no haze and 4 representing maximum opacity. According to the meta-analysis, the overall PUMD of the corneal haze score was −0.20 (95% CI, −0.29 to −0.12), indicating a statistically significant difference between the steroid and nonsteroid groups in favor of the steroid group. Subgroup analysis showed

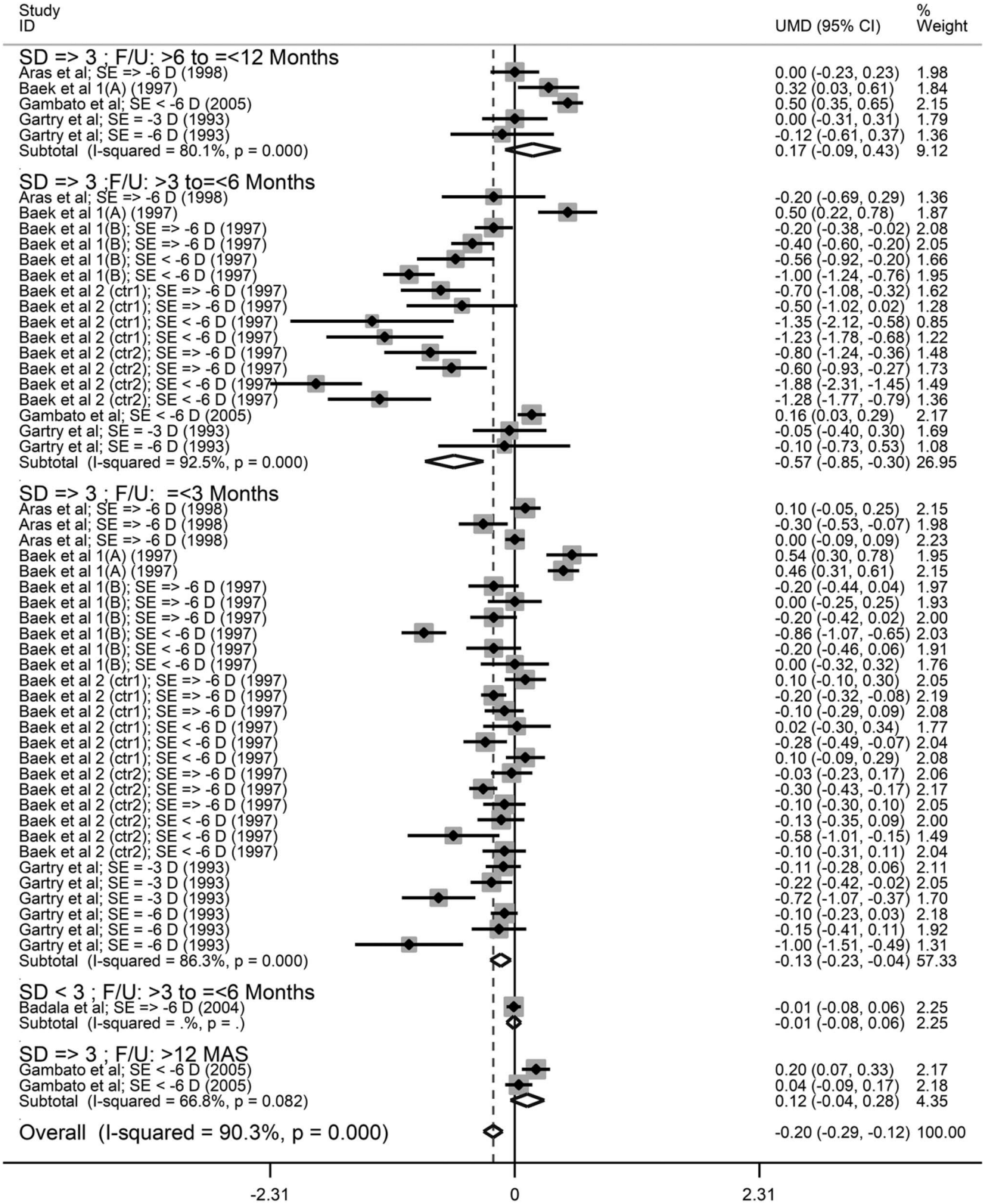

Figure 3. PUMD of the haze score based on the random-effects model in different steroid duration and measurement time groups. The midpoint of each line segment shows the estimate, the length of the line segment indicates the 95% CI in each study, and the diamond mark illustrates the PUMD of the haze score (F/U = follow-up; PUMD = pooled unstandardized mean difference; SD = steroid duration; months = months postoperatively).

a lower mean haze score at least 6 months postoperatively in patients who received steroids for at least 3 months postoperatively, although this finding was not statistically significant. Figure 3 demonstrates the PUMD of the haze score in different steroid duration and follow-up subgroups.

The mean difference of the haze score (intervention minus control) was statistically significant in 2 subgroups, −0.57 (−0.85 to −0.30) for steroid duration ≥ 3 and follow-up > 3 to ≤ 6 months and −0.13 (−0.23 to −0.04) for steroid duration ≥ 3 and follow-up ≤ 3 months. The difference was not significant in other subgroups. Analysis of corneal haze based on preoperative SE showed a significant difference in both subgroups of ≥−6 D and <−6 D, which was higher in <−6 D. The PUMD of the haze score was −0.18 (−0.25 to −0.11) and −0.39 (−0.61 to −0.17) in ≥−6 D and <−6 D, respectively (Figure 4).

Estimate of Postoperative Spherical Equivalent

The overall PUMD of postoperative SE between the steroid and control groups (intervention minus control) was estimated at 0.43 (95% CI, 0.21 to 0.66), indicating the effect of steroid on prevention of myopic regression. Figure 5 shows the PUMD of postoperative SE in different steroid duration and follow-up subgroups. The difference was above zero in subgroups of steroid duration ≥ 3; follow-up ≤ 6 months and steroid duration < 3; and follow-up > 6 months, indicating the positive effect of steroids on postoperative SE (0.52 [0.27 to 0.77] and 0.46 [0.01 to 0.91], respectively). No significant difference was observed in the other subgroup (steroid duration ≥ 3; follow-up > 6 months).

Analysis of the PUMD of postoperative SE in participants with low (≥−6 D) to moderate myopia (<−6 D) showed positive effects of steroids on prevention of myopia regression (0.40 [0.19 to 0.61] and 0.97 [0.43 to 1.52], respectively) (Figure 6). All subgroup analyses are presented in Figure 7.

Heterogeneity and Meta-regression

According to meta-regression results, the following variables had significant effects on heterogeneity in the mean difference of the haze score between studies: study

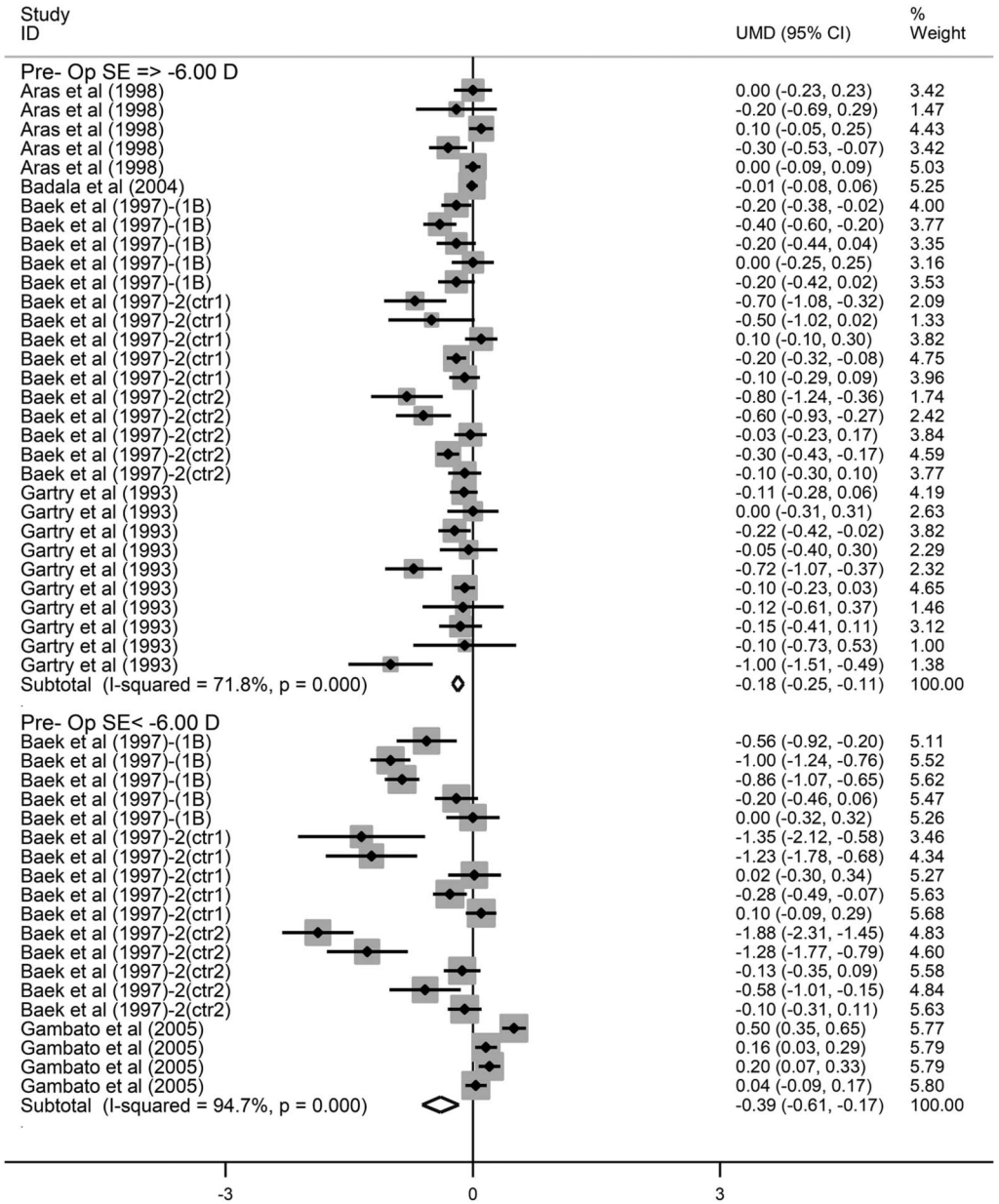

Figure 4. Pooled unstandardized mean difference of the haze score based on the random-effects model in different subgroups of preoperative SE (SE = spherical equivalent).

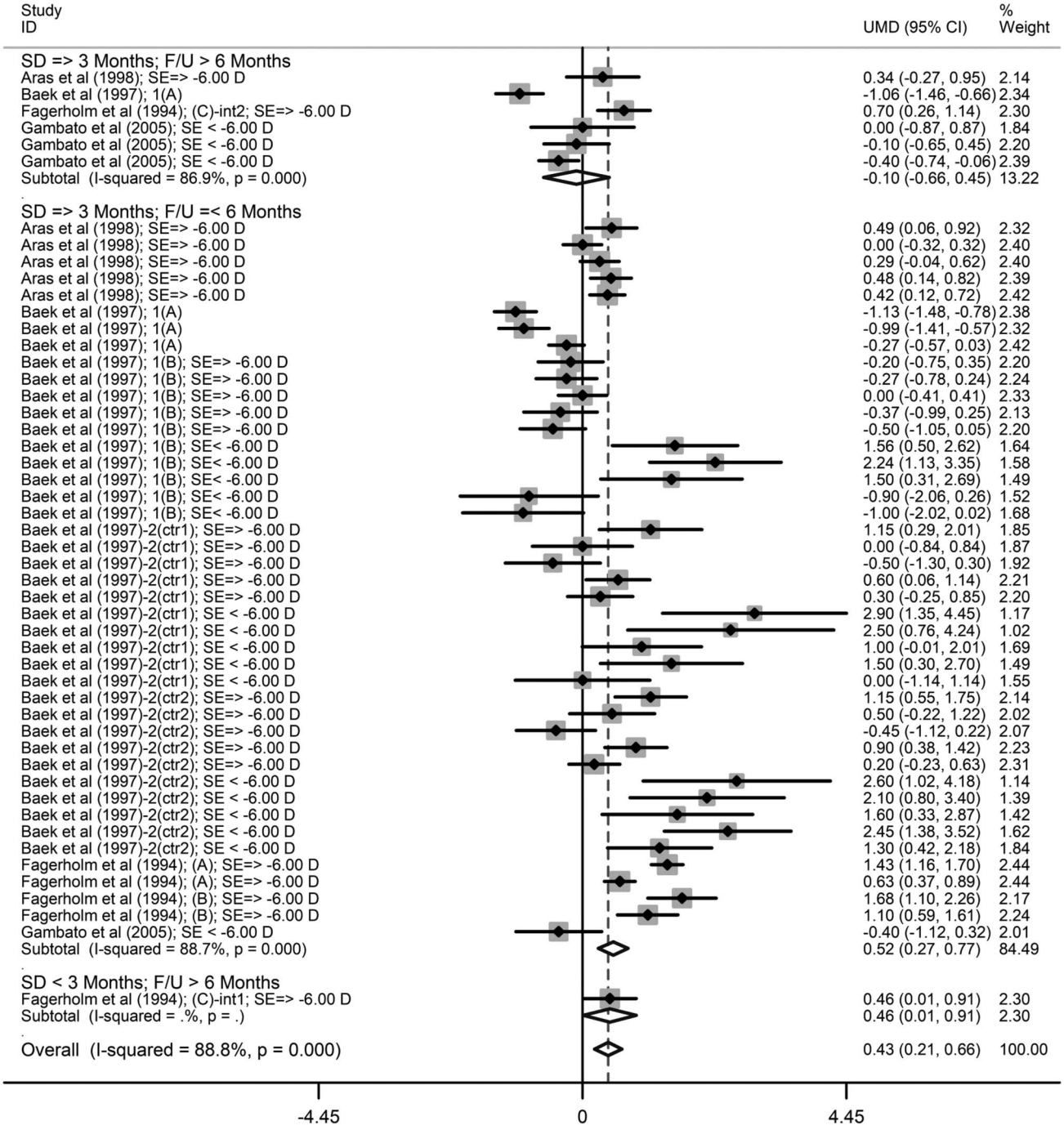

Figure 5. PUMD of postoperative SE based on the random-effects model in different steroid duration and measurement time groups. The midpoint of each line segment shows the estimate, the length of the line segment indicates the 95% CI in each study, and the diamond mark illustrates the PUMD of postoperative SE (PUMD = pooled unstandardized mean difference; SD = steroid duration; SE = spherical equivalent; months = months postoperatively).

design (0.364; $P = .001$), study quality (0.033; $P = .040$), and total sample size (0.004; $P < .001$). In other words, the mean difference of the haze score was higher in historical cohorts and higher quality studies with larger sample sizes. Heterogeneity in postoperative SE was due to some variables such as quality (−0.084; $P = .001$) and total sample size (−0.005; $P < .017$). Publication year (−0.105; $P = .045$) and ablation diameter (−0.153; $P = .048$) also had a borderline significant effect. Newer studies, high-quality studies, and studies with larger sample sizes and ablation diameters reported lower myopic regression postoperatively (Tables 1 and 2). The effect of sample size on the haze score and postoperative mean difference is demonstrated in Figures 8 and 9, respectively.

DISCUSSION

Corneal haze is one of the most feared complications of PRK surgery, which develops because of the normal wound healing

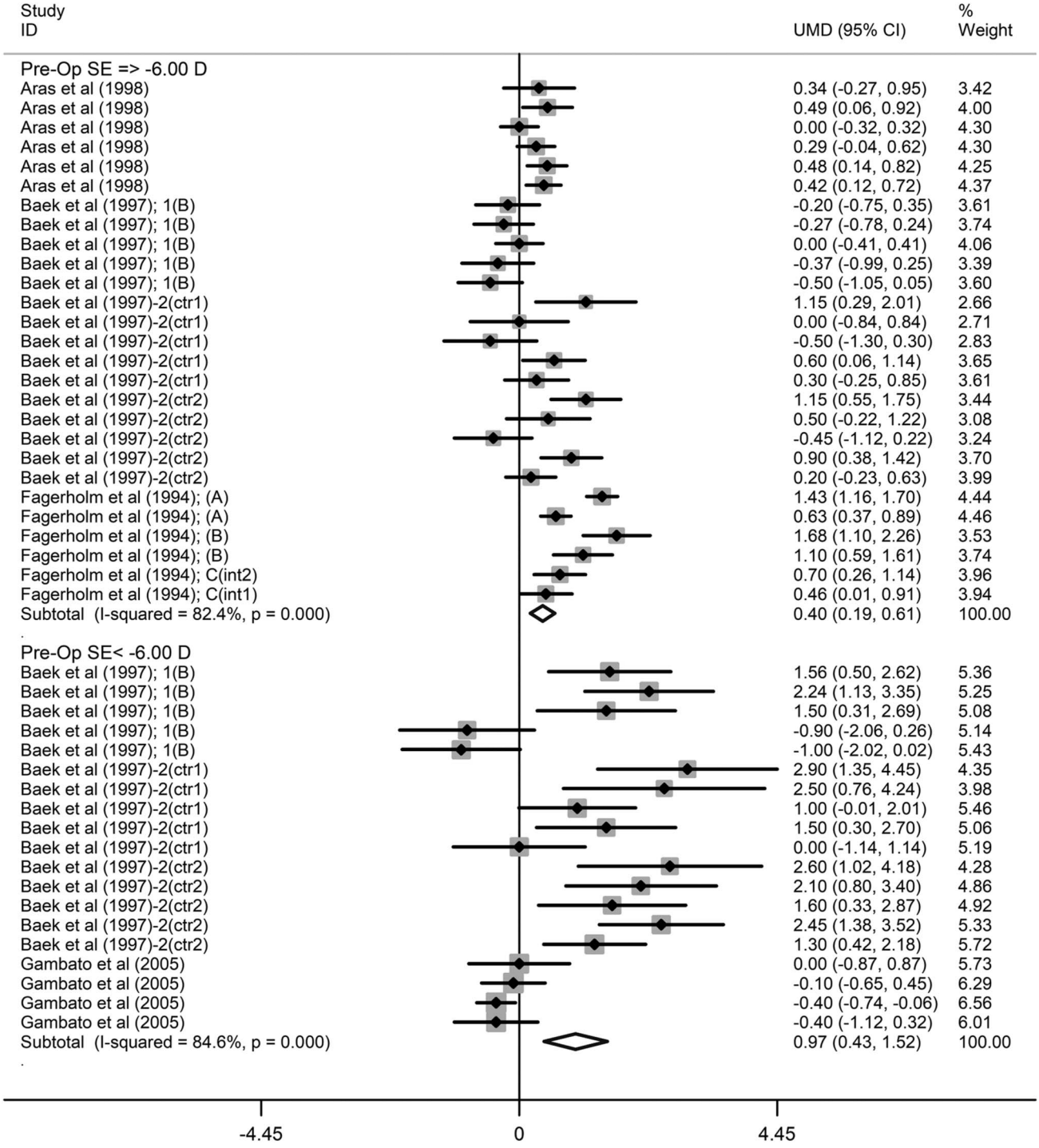

Figure 6. Pooled unstandardized mean difference of postoperative SE based on the random-effects model in different subgroups of preoperative SE (SE = spherical equivalent).

process. After epithelial injury and basement membrane destruction, inflammatory mediators such as cytokines and growth factors are released from epithelial cells that activate differentiation of keratocytes into myofibroblasts. Myofibroblasts express different extracellular matrix. Disorganized matrix material including abnormal collagen fibers and other substances remodels the stromal tissue, which is associated with decreased corneal transparency and corneal haze development.[36–40] Corticosteroids are anti-inflammatory agents that maintain the transparency of the cornea through inhibition of the immune response and collagen synthesis. Corticosteroids are applied postoperatively to avoid corneal haze and myopic regression after PRK.

This meta-analysis evaluated the effect of steroid administration on the postoperative corneal haze score and SE after refractive surgical procedures such as PRK and laser subepithelial keratomileusis. The overall results suggested that steroid administration resulted in lower

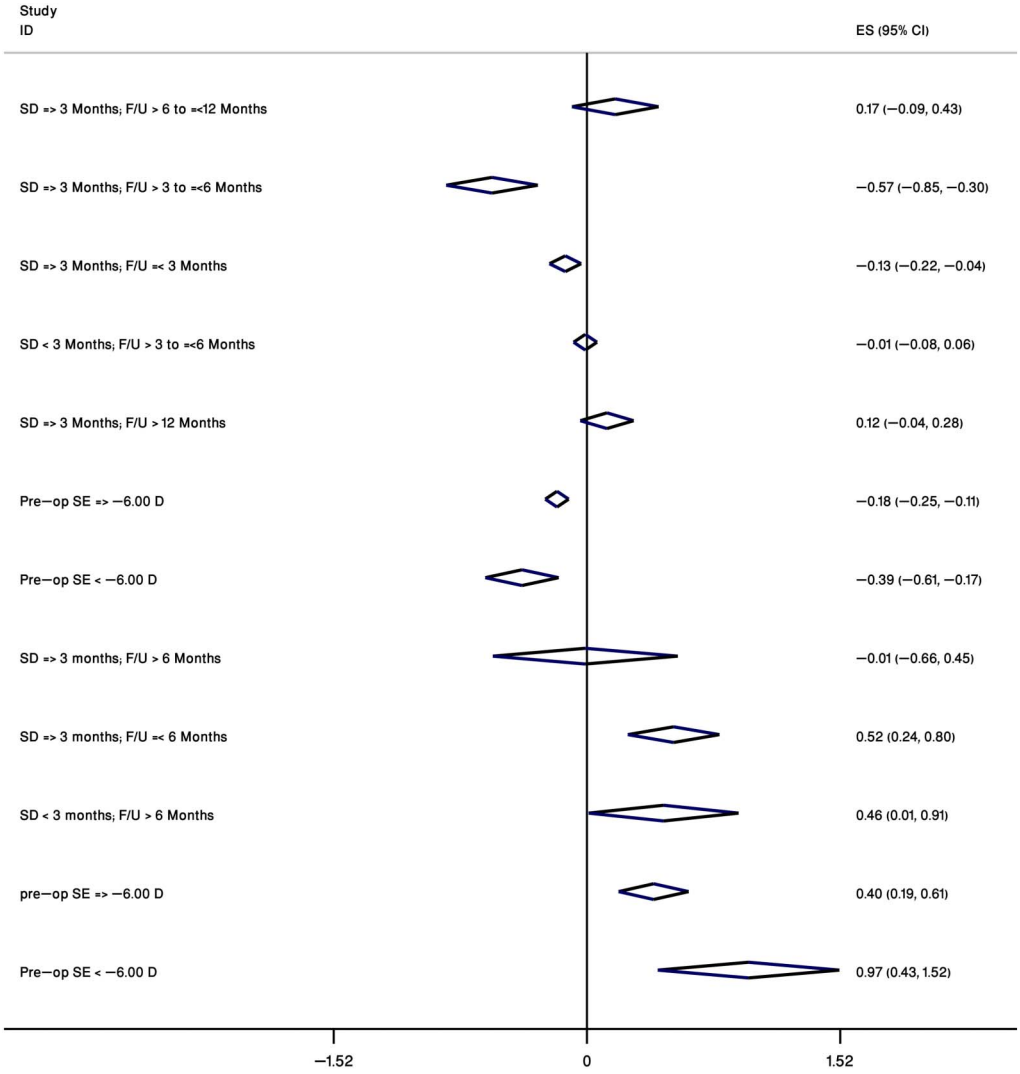

Figure 7. PUMD in different subgroups based on the random-effects model. Diamond mark illustrates the PUMD (PUMD = pooled unstandardized mean difference).

haze scores, but interpretation of the results could be influenced by several factors such as lack of available studies in this area.

There are 2 types of corneal haze after refractive surgery. The first type occurs 1 to 3 months postoperatively and lasts for 12 months. The other type, with a late onset, develops between 2 and 5 months postoperatively and may persist for 3 years.[14] As shown in Figure 3, only 6 studies reported the data of haze and entered the meta-analysis, of which only 3 provided the results of the 12-month follow-up. However, the results of follow-up for more than 3 months postoperatively showed no significant difference between the steroid and control groups. Similarly, although the overall postoperative myopic regression was higher in control groups compared with steroid groups, it was limited to 6-month follow-ups.

Table 1. Results of univariate meta-regression analysis on the heterogeneity of the determinants for the unstandardized mean difference of the haze score.

Variable	Coefficient	95% CI	*P* Value
Age, y	0.005	−0.024 to 0.035	.717
Spherical equivalent, D	−0.157	−0.412 to 0.097	.220
Design	0.364	0.149 to 0.580	.001*
Publication year	0.038	−0.002 to 0.079	.064
Ablation diameter	0.055	−0.004 to 0.115	.067
Quality assessment	0.033	0.001 to 0.065	.040*
Total sample size	0.004	0.002 to 0.006	.000*

Ablation diameter: 1 = 4.0 mm; 2 = 5.0 mm; 3 = 6.0 mm; 4 = 6.0 to 9.0 mm; 5 = 7.0 mm
SE: 1 ≤ −6 D; 2 > −6 D.
Design: 1 = RCT; 2 = historical cohort.
Quality assessment: score.

Table 2. Results of univariate meta-regression analysis on the heterogeneity of the determinants for the unstandardized mean difference of postoperative SE.

Variable	Coefficient	95% CI	*P* Value
Age, y	0.049	−0.063 to 0.163	.383
SE, D[†]	0.503	−0.040 to 1.048	.069
Design	−0.133	−0.462 to 0.196	.421
Publication year	−0.105	−0.208 to −0.002	.045*
Ablation diameter	−0.153	−0.306 to 0.001	.048*
Quality assessment, score	−0.084	−0.134 to −0.035	.001*
Total sample size	−0.005	−0.009 to −0.000	.017*

RCT = randomized clinical trial; SE = spherical equivalent
Ablation diameter: 1 = 4.3 mm; 2 = 5.0 mm; 3 = 6.0 mm; 4 = 7.0 mm.
Design: 1 = RCT; 2 = historical cohort.
[†]SE: 1 ≤ −6 D; 2 > −6 D.

Most of the studies were published at least 20 years ago and did not apply mitomycin during the procedure. Mitomycin C, as a genotoxic antibiotic, inhibits cell mitosis and protein synthesis through blocking the synthesis of DNA. This antibiotic can reduce PRK complications associated with haze and refractive error regression via obstructing the transformation of keratocytes into myofibroblasts.[24,41,42] Meta-regression results also proved the effect of publication year. Smaller differences in myopic regression were observed between groups in newer studies (β = −0.105; *P* = .045).

The design of the studies included in this meta-analysis as another factor affecting the results. The study design was one of the sources of heterogeneity in the mean corneal haze score between the steroid and control groups (β = 0.364; *P* = .001). In other words, steroid administration was more effective in studies with a historical cohort design than RCTs. Randomization and blinding, which enhance the study results, are not used in cohort designs.

A small ablation diameter is a known risk factor for corneal haze development in some studies.[9,10] The results of this meta-analysis showed that a larger ablation diameter could increase the SE difference between groups; in other words, in larger ablation diameters, the role of steroids could be weaker in prevention of postoperative haze.

High myopic ablations (higher ablation depth) generate more myofibroblasts than low to moderate myopic ablations; therefore, they could result in more postoperative haze and myopic regression.[43,44] The results of our study confirmed that steroids were more effective in higher myopic ablations (more than 6 D).

Corneal haze formation was more probable with early excimer laser instruments. Recent generations with small beams provide more uniform corneal profiles and decrease the release of proinflammatory cytokine, which leads to better visual outcomes and sooner refractive stability.[45–47] Broad beam lasers were used in most of the included studies in this meta-analysis, which belong to the older generations, and only 2 studies applied flying spot systems. Because of the limited number and variety of these studies, we could not investigate the effect of the type of excimer machine on corneal haze development.

UV radiation exposure has been reported as a risk factor for haze formation after surface ablation.[12,48] Exposure to UV radiation is very high in some places such as tropical

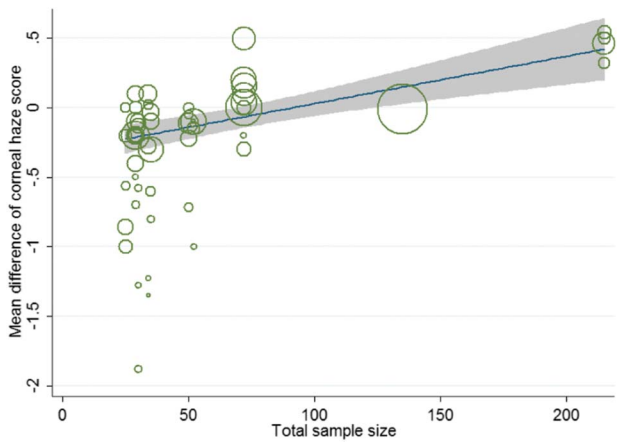

Figure 8. Results of meta-regression on the relationship between the unstandardized mean difference of the haze score and the total sample size. Circle size represents the precision of each study. There is no significant relationship between the unstandardized mean difference of the haze score and the total sample size.

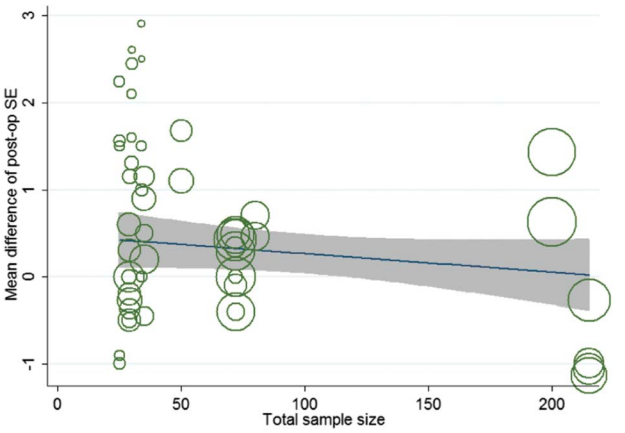

Figure 9. Results of meta-regression on the relationship between the unstandardized mean difference of postoperative SE and the total sample size. Circle size represents the precision of each study. There is a significant relationship between the unstandardized mean difference of postoperative SE and the total sample size. The mean difference of postoperative SE relatively decreased with the increase in the sample size (SE= spherical equivalent).

countries. However, studies included in this meta-analysis were conducted in Asian and European countries, and geographical location was not statistically significant in meta-regression analysis.

The most important limitation of this meta-analysis was scares of the relevant studies, especially RCTs, having both steroid and control groups. Another limitation was lack of high-quality and new articles that made a robust conclusion impossible. Some of these few available studies reported their data only by figures that were inappropriate data to analyze. Finally, most of the studies reported the 6-month follow-up results, and few of them followed their patients until 12 months.

In conclusion, the results of this systematic review and meta-analysis suggest that steroids can reduce postoperative corneal haze and myopic regression during the first 6 months after refractive surgery, but the results are similar in long-term follow-up studies. Long duration post-refractive surgery steroid administration seems to be unnecessary in low and moderate myopia compared with high myopia. A randomized clinical trial with advanced and newer machines might clarify the optimum duration of postoperative steroids more precisely.

WHAT WAS KNOWN

- Topical steroids are administered routinely after photorefractive keratectomy from weeks to months to prevent corneal haze and myopic regression.

WHAT THIS PAPER ADDS

- Steroids can reduce postoperative corneal haze and myopic regression during the first 6 months after refractive surgery, but the results are similar in long-term follow-ups.
- Long duration post-refractive surgery steroid administration seems to be unnecessary in low and moderate myopia compared with high myopia.

REFERENCES

1. Woreta FA, Gupta A, Hochstetler B, Bower KS. Management of post-photorefractive keratectomy pain. Surv Ophthalmol 2013;58:529–535
2. Mysore N, Krueger R. Advances in refractive surgery: May 2013 to June 2014. Asia Pac J Ophthalmol 2015;4:112–120
3. Alio JL, Javaloy J. Corneal inflammation following corneal photoablative refractive surgery with excimer laser. Surv Ophthalmol 2013;58:11–25
4. Moller-Pedersen T, Li HF, Petroll WM, Cavanagh HD, Jester JV. Confocal microscopic characterization of wound repair after photorefractive keratectomy. Invest Ophthalmol Vis Sci 1998;39:487–501
5. Murueta-Goyena A, Canadas P. Visual outcomes and management after corneal refractive surgery: a review. J Optom 2018;11:121–129
6. Jester JV, Petroll WM, Cavanagh HD. Corneal stromal wound healing in refractive surgery: the role of myofibroblasts. Prog Retin Eye Res 1999;18:311–356
7. Goggin M, Foley-Nolan A, Algawi K, O'Keefe M. Regression after photorefractive keratectomy for myopia. J Cataract Refract Surg 1996;22:194–196
8. Netto MV, Mohan RR, Sinha S, Sharma A, Dupps W, Wilson SE. Stromal haze, myofibroblasts, and surface irregularity after PRK. Exp Eye Res 2006;82:788–797
9. Corbett MC, O'Brart DP, Warburton FG, Marshall J. Biologic and environmental risk factors for regression after photorefractive keratectomy. Ophthalmology 1996;103:1381–1391
10. Rajan MS, O'Brart D, Jaycock P, Marshall J. Effects of ablation diameter on long-term refractive stability and corneal transparency after photorefractive keratectomy. Ophthalmology 2006;113:1798–1806
11. Thomas KE, Brunstetter T, Rogers S, Sheridan MV. Astigmatism: risk factor for postoperative corneal haze in conventional myopic photorefractive keratectomy. J Cataract Refract Surg 2008;34:2068–2072
12. Stojanovic A, Nitter TA. Correlation between ultraviolet radiation level and the incidence of late-onset corneal haze after photorefractive keratectomy. J Cataract Refract Surg 2001;27:404–410
13. Tabbara KF, El-Sheikh HF, Sharara NA, Aabed B. Corneal haze among blue eyes and brown eyes after photorefractive keratectomy. Ophthalmology 1999;106:2210–2215
14. Margo JA, Munir WM. Corneal haze following refractive surgery: a review of pathophysiology, incidence, prevention, and treatment. Int Ophthalmol Clin 2016;56:111–125
15. Marques EF, Leite EB, Cunha-Vaz JG. Corticosteroids for reversal of myopic regression after photorefractive keratectomy. J Refract Surg 1995;11:S302–S308
16. Caubet E. Course of subepithelial corneal haze over 18 months after photorefractive keratectomy for myopia [corrected]. Refractive Corneal Surg 1993;9:S65-S70
17. Gartry DS, Kerr Muir M, Marshall J. The effect of topical corticosteroids on refraction and corneal haze following excimer laser treatment of myopia: an update. A prospective, randomised, double-masked study. Eye 1993;7(pt 4):584–590
18. O'Brart DP, Lohmann CP, Klonos G, Corbett MC, Pollock WS, Kerr-Muir MG, Marshall J. The effects of topical corticosteroids and plasmin inhibitors on refractive outcome, haze, and visual performance after photorefractive keratectomy. A prospective, randomized, observer-masked study. Ophthalmology 1994;101:1565–1574
19. Tengroth B, Fagerholm P, Soderberg P, Hamberg-Nyström H, Epstein D. Effect of corticosteroids in postoperative care following photorefractive keratectomies. Refract Corneal Surg 1993;9:S61–S64
20. Buhren J, Nagy L, Swanton JN, Kenner S, MacRae S, Phipps RP, Huxlin KR. Optical effects of anti-TGFbeta treatment after photorefractive keratectomy in a cat model. Invest Ophthalmol Vis Sci 2009;50:634–643
21. Schipper I, Suppelt C, Gebbers JO. Mitomycin C reduces scar formation after excimer laser (193 nm) photorefractive keratectomy in rabbits. Eye 1997;11(pt 5):649–655
22. Carones F, Vigo L, Scandola E, Vacchini L. Evaluation of the prophylactic use of mitomycin-C to inhibit haze formation after photorefractive keratectomy. J Cataract Refract Surg 2002;28:2088–2095
23. Kaiserman I, Sadi N, Mimouni M, Sela T, Munzer G, Levartovsky S. Corneal breakthrough haze after photorefractive keratectomy with mitomycin C: incidence and risk factors. Cornea 2017;36:961–966
24. Chen SH, Feng YF, Stojanovic A, Wang QM. Meta-analysis of clinical outcomes comparing surface ablation for correction of myopia with and without 0.02% mitomycin C. J Refract Surg 2011;27:530–541
25. Corbett MC, O'Brart DP, Marshall J. Do topical corticosteroids have a role following excimer laser photorefractive keratectomy? J Refract Surg 1995;11:380–387
26. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–269
27. Ferrari M. Use of topical nonsteroidal anti-inflammatory drugs after photorefractive keratectomy. J Refract Corneal Surg 1994;10:S287–S289
28. Arshinoff SA, Mills MD, Haber S. Pharmacotherapy of photorefractive keratectomy. J Cataract Refract Surg 1996;22:1037–1044
29. Baek SH, Chang JH, Choi SY, Kim WJ, Lee JH. The effect of topical corticosteroids on refractive outcome and corneal haze after photorefractive keratectomy. J Refract Surg 1997;13:644–652
30. Baek SH, Choi SY, Chang JH, Wee WR, Lee JH. Short-term effects of flurbiprofen and diclofenac on refractive outcome and corneal haze after photorefractive keratectomy. J Cataract Refract Surg 1997;23:1317–1323
31. Gartry DS, Kerr Muir GM, Marshall J. The effect of topical corticosteroids on refraction and corneal haze following excimer laser treatment of myopia: an update. A prospective, randomised, double-masked study. Eye 1993;7:584–590
32. Aras C, Özdamar A, Aktunç R, Erçikan C. The effects of topical steroids on refractive outcome and corneal haze, thickness, and curvature after photorefractive keratectomy with a 6.0-mm ablation diameter. Ophthalmic Surg Lasers 1998;29:621–627
33. Badalà F, Fioretto M, Macrì A. Effect of topical 0.1% indomethacin solution versus 0.1% fluorometholone acetate on ocular surface and pain control following laser subepithelial keratomileusis (LASEK). Cornea 2004;23:550–553
34. Fagerholm P, Hamberg-Nyström H, Tengroth B, Epstein D. Effect of postoperative steroids on the refractive outcome of photorefractive keratectomy for myopia with the Summit excimer laser. J Cataract Refract Surg 1994;20:212–215

35. Gambato C, Ghirlando A, Moretto E, Busato F, Midena E. Mitomycin C modulation of corneal wound healing after photorefractive keratectomy in highly myopic eyes. Ophthalmology 2005;112:208–218
36. Kaji Y, Obata H, Usui T, Soya K, Machinami R, Tsuru T, Yamashita H. Three-dimensional organization of collagen fibrils during corneal stromal wound healing after excimer laser keratectomy. J Cataract Refract Surg 1998;24:1441–1446
37. Wilson SE. Analysis of the keratocyte apoptosis, keratocyte proliferation, and myofibroblast transformation responses after photorefractive keratectomy and laser in situ keratomileusis. Trans Am Ophthalmol Soc 2002;100:411–433
38. Tomas-Juan J, Murueta-Goyena Larranaga A, Hanneken L. Corneal regeneration after photorefractive keratectomy: a review. J Optom 2015;8:149–169
39. Chaurasia SS, Kaur H, de Medeiros FW, Smith SD, Wilson SE. Dynamics of the expression of intermediate filaments vimentin and desmin during myofibroblast differentiation after corneal injury. Exp Eye Res 2009;89:133–139
40. Winkler von Mohrenfels C, Reischl U, Lohmann CP. Corneal haze after photorefractive keratectomy for myopia: role of collagen IV mRNA typing as a predictor of haze. J Cataract Refract Surg 2002;28:1446–1451
41. Santhiago MR, Netto MV, Wilson SE. Mitomycin C: biological effects and use in refractive surgery. Cornea 2012;31:311–321
42. Coelho LM, Sieiro RO. Mitomycin C 0.02 and 0.002% efficacy in preventing haze after photorefractive keratectomy. Int Ophthalmol. 2019;39:341–345
43. Taylor SM, Fields CR, Barker FM, Sanzo J. Effect of depth upon the smoothness of excimer laser corneal ablation. Optom Vis Sci 1994;71:104–108
44. Tang X, Liao Z. A clinical study of correlation between ablation depth and corneal subepithelial haze after photorefractive keratectomy [in Chinese]. Chin J Ophthalmol 1997;33:204–206
45. Fiore T, Carones F, Brancato R. Broad beam vs. flying spot excimer laser: refractive and videokeratographic outcomes of two different ablation profiles after photorefractive keratectomy. J Refract Surg 2001;17:534–541
46. Muller B, Boeck T, Hartmann C. Effect of excimer laser beam delivery and beam shaping on corneal sphericity in photorefractive keratectomy. J Cataract Refract Surg 2004;30:464–470
47. Vestergaard AH, Hjortdal JO, Ivarsen A, Work K, Grauslund J, Sjølie AK. Long-term outcomes of photorefractive keratectomy for low to high myopia: 13 to 19 years of follow-up. J Refract Surg 2013;29:312–319
48. Nagy ZZ, Hiscott P, Seitz B, Shlötzer-Schrehardt U, Simon M Jr, Süveges I, Naumann GO. Ultraviolet-B enhances corneal stromal response to 193-nm excimer laser treatment. Ophthalmology 1997;104:375–380

Disclosures: *None of the authors has a financial or proprietary interest in any material or method mentioned.*