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ORIGINAL ARTICLE

Analysis quantitative and qualitative of the tear film in patients undergoing PRK and LASIK with femtosecond

Análise quantitativa e qualitativa do filme lacrimal nos pacientes submetidos a PRK e LASIK com femtossegundo

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ABSTRACT

Purpose: To evaluate tear film stability, ocular surface staining and tear secretion in patients undergoing PRK and femtosecond laser LASIK. **Methods:** Twenty eyes of 10 patients submitted to femtosecond laser LASIK and 11 eyes of the 6 patients submitted do PRK underwent tear film break-up time (TBUT), Schirmer's basal and lissamine green staining measurements pre and postoperatively on days 15 (PO 15) and 30 (PO 30). **Results:** When grouping all eyes TBUT was reduced on PO 15 (p=0.025) and on PO 30 (p=0.001) compared to preoperative values. No difference was found between PO 15 and PO 30 (p=0.219). Compared to preoperative measurements, lissamine green test demonstrated a significant increase in score on PO 15 (p=0.021) and a significant reduction on PO 30 (p=0.010), when both groups were analyzed together (all 42 eyes). No changes in Schirmer's basal test were detected in all 3 time periods (p=0.107). TBUT, lissamine green and Schirmer's basal measurements were no different in all 3 time periods when both groups (PRK and femtosecond laser LASIK) were compared. **Conclusion:** TBUT and lissamine green measurements were altered after refractive surgery regardless the technique (PRK or femtosecond laser LASIK). When comparing one technique to the other, no difference was found in all measurements.

Keywords: Dry eye syndromes; Tears; Refractive surgical procedures; Keratomileusis, laser in situ; Corneal surgery, laser; Photorefractive keratectomies

RESUMO

Objetivo: *Analisar a secreção lacrimal, coloração da superfície ocular e estabilidade do filme lacrimal em indivíduos submetidos à cirurgia de PRK e LASIK com laser de femtossegundo (femto LASIK).* ***Métodos:*** *Vinte olhos de 10 pacientes submetidos à técnica de Femto LASIK e 11 olhos de 6 pacientes submetidos à técnica de PRK foram estudados de forma prospectiva, longitudinal e intervencionista. Tempo de rotura do filme lacrimal (TRFL), teste de Schirmer basal e coloração da superfície ocular com lissamina verde foram analisados no pré-operatório (pré), no 15º e no 30º dia pós-operatório (15º pós e 30º pós, respectivamente).* ***Resultados:*** *Agrupando todos os olhos, observou-se que o TRFL reduziu-se de forma estatisticamente significante no 15º pós em relação ao valor pré-operatório (p=0,025), mantendo-se reduzido no 30º pós (p= 0,001); não houve diferença estatisticamente significativa entre o 15º pós e o 30º pós (p=0,219). No teste da lissamina verde, houve aumento significativo desse escore, no 15º pós em relação ao período pré-operatório (p=0,021), havendo, posteriormente, redução no 30º pós (p=0,010). No teste de Schirmer basal, não foi detectada mudança estatisticamente significante ao longo dos três momentos (p=0,107). Comparando-se os testes TRFL, lissamina verde ou Schirmer basal, nos dois grupos estudados (PRK e LASIK), não houve diferença estatisticamente significante em nenhum dos três momentos (pré, 15º pós e 30º pós).* ***Conclusão:*** *Evidenciou-se alteração do filme lacrimal nos pacientes submetidos à cirurgia refrativa, quando foram utilizados os testes de TRFL e lissamina verde. Nas duas técnicas empregadas, não houve diferença estatisticamente significante de alteração do filme lacrimal, quando comparadas entre si (PRK e LASIK).*

Descritores: *Síndrome do olho seco; Lágrimas; Procedimentos cirúrgicos refrativos; Ceratomileuse assistida por excimer laser in situ; Cirurgia da córnea a laser; Ceratectomia fotorrefrativa*

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Introduction

Refractive surgery techniques have been continually evolving, with photorefractive keratectomy (PRK) and laser-assisted in situ keratomileusis (LASIK) being the two most commonly used techniques.Both procedures are considered safe and produce photoablation of corneal tissue, thus changing its refractive power.[1,2] Studies show that LASIK is the most common refractive procedure for mild to moderate myopia, and there are different devices for creating the corneal flap.[2,3] Mechanical microkeratomes are the most used, promoting rapid visual recovery with minimal discomfort. An alternative is femtosecond laser, an automated device for creating a corneal flap; it is safer, more reliable and predictable, and may reduce the risk of epithelial defects and striae on the corneal flap.[4,5]

In clinical practice, many patients complain of dry eye sensation after refractive surgery.[1,2]Attention should be given to this matter, because dry eye syndrome can severely affect a patient's quality of life.For example, patients with moderate to severe dry eye report quantitative quality of life scores similar to patients with moderate to severe angina or patients undergoing dialysis.Furthermore, dry eye is the main cause for dissatisfaction after refractive surgery.[2,5,6]

Several studies based on quantitative tests have demonstrated an increased incidence of dry eye in the first monthsafter refractive surgery.[1,2,5-8] Several theories attempt to explain the onset of the syndrome after refractive surgery.There is a complex interaction between afferent sensory nerves of the ocular surface and autonomic efferent nerves of the lacrimal gland which modulate tear secretion.Any factor interfering with that relationship can cause dry eye.[1,5] Sensory nerves of the corneaarisingfrom the ophthalmic and maxillary branches of the trigeminal nerve penetrate through the limbus, forming a thick nerve bundle in the anterior third of the cornea; those nerves then penetrate Bowman's layer and form the epithelial-subepithelial plexus between the basal epithelial cells and Bowman's layer.When these nerves are cut while creating the corneal flap in LASIK and during photoablation in PRK, this harmony is affected, which can cause dry eye.[1,2,5-8] In addition, postoperative inflammation near the nerve endings could stimulate the production of cytokines, thus exacerbating the condition.Furthermore, both refractive surgery techniques alter the corneal curvature, changing the relationship betweenthe tear surface and the eyelids during blinking and affecting tear distribution.[5] Another proposed pathophysiological mechanism is based on the observation that the number of goblet cells can be decreasedin patients submitted to LASIK, probably due to direct damage by the suction deviceduring the creation of the corneal flap (using either a microkeratome or femtosecond laser).[4,5]

The aim of this study was to determine whether patients undergoing PRK and LASIK with femtosecond laser exhibit postoperativequantitative changes in tear production or changes in tear film stability and whether any of the two techniques is associated with a higher incidence of such changes, using the following tests:tear film breakup time (TFBU), the basal Schirmer test, and the lissamine green test.

Methods

A prospective, longitudinal intervention study was performed on 31 eyes (16 patients), of which 20 eyes (10 patients) were submitted to LASIK with femtosecond laser and 11 eyes (6 patients) underwent PRK.Patients were seen at the Refractive Surgery Unit of Santa Casa de Misericórdia Hospital, São Paulo, between August 2012 and May 2013; all procedures were performed on June 27, 2013 at the Eye Clinic Day Hospital, a private eye clinic, free of any charge.Patients with contact lensesdiscontinued their useone month before surgery.

The study was approved by the Research Ethics Committee of Santa Casa de Misericórdia under number 261728.

Inclusion criteria weresubjects over 21 years of age with refractive errorsthat had been stable for at least one year, with a spherical equivalent between -1.50 and - 6.00 dioptres and less than 2.00 cylindrical dioptres, normal corneal topography, and without other eye diseases.

Exclusion criteria werepatientsunable to attend follow-up visits, previous eye surgery, systemic diseases and/or eye diseases that could alter the tear film, and patients using drugs that could interfere with tear production.

The decision to use PRK or LASIK was based on each patient's corneal thickness and refractive error.

Patients underwent the following tests a week before surgery (Pre), on the 15th postoperative day (15 PO), and on the 30thPO day (30 PO): TFBU,the basal Schirmer test, and the lissamine green test.All tests were performed in the same environment, in a closed room.

TFBU was performed instilling one drop of fluorescein on the conjunctival sac.The patient was instructed to blink several times to distribute the fluorescein evenly, being then submitted to slit lamp examination with a cobalt blue filter.A digital stopwatch was used to count the time (in seconds) between the last blink and the appearance of the first dry spot.

Lissamine green staining was then performed by placing the lissamine tape in contact with the lacrimal meniscus of the lower conjunctival sac, with analysis 2 minutes laterusing the van Bijsterveld classification.The palpebral fissure was divided into 3 areas:lateral bulbar conjunctiva, cornea, and medial bulbar conjunctiva.In each area, the following classification was used:0, no staining; 1, isolated thin spots; 2, grouped coarse spots; 3,plaque.The sum for each of these areas was then calculated, producing the final score (range, 0-9).

After 10 minutes the basal Schirmer test was performed.A drop of anaesthetic was instilled in the inferior fornix.A strip of Whatman filter paper No.41, 5-mm wide and 35-mm long, was then placed between the middle and lateral thirds of the lower eyelid.After 5 minutes, the strip was removed and the moist part of the filter paper was measured.

Surgical technique

WaveLight EX500™ (Alcon) excimer laser was used for PRK.Bandage contact lenses were applied after the procedure for seven days.Patients were prescribed moxifloxacin 0.5% (Vigamox™ Alcon) eye drops every 6 hours for 7 days, ketorolac tromethamine (Acular™, Alcon) eye drops every 6 hours for 3 days, and prednisolone acetate0.12% (Ster MD™, Genom), which was phased out over six weeks.

In patients submitted to LASIK, the corneal flap was created using the LDV Z6™ (Ziemer) femtosecond laser with a 110-µm thickness, and photoablation was done using the WaveLight EX500™ (Alcon) excimer laser.Patients were prescribed combined eye drops of moxifloxacin 0.5% + dexamethasone 0.1% (Vigadexa™, Alcon) for seven days.

Results

The following tests were used for statistical analysis:

- Fisher's exact test for comparing the gender distribution of patients between the two groups (PRK and LASIK);
- Student's t-test for independent samples for comparing the age (years) of patients between the two groups;
- ANOVA with blocks for comparing the results of TFBU (seconds), lissamine green (score), and basal Schirmer test (millimetres) at the different time points (Pre, 15 PO and 30 PO), as well as the LSD method for multiple comparisons when necessary;
- ANOVA with repeated measures for comparing the results of TRFL, lissamine green and basal Schirmer test at the different time points (Pre, Post 15 and Post 30)between the two groups (PRK vs. LASIK).

In all conclusions reached through inferential analysis a significance level of p = 5% was adopted.

Table 1

Distribution of patients submitted to PRK and LASIK according to gender and age.

	PRK	LASIK	Total	p-value
Genre (n%)				
Female	5 83.3	7 70.0	12 75.0	>0.999[a]
Male	1 16.7	3 30.0	4 25.0	
Total	6 100.0	10 100.0	16 100.0	
Age (years) 0				
N	6	10	16	0.728[b]
Mean	33.7	32.1	32.7	
Median	33.5	32.0	32.0	
Minimum	26.0	22.0	22.0	
Maximum	45.0	52.0	52.0	
Standard-deviation	7.6	9.0	8.3	

[a]Fisher's exact test, [b]Student's t-test for independent samples.

In the PRK group 83.3% of patients were female, compared to 70% in the LASIK group.There were no statistically-significant differences between groups regarding gender (p >0.999).Mean age was 33.7 ± 7.6 in the PRK group and 32.1 ± 9.0 in the LASIK group, and the difference was not significant (p = 0.728). (Table 1, Charts 1 and 2).

Chart 1

Distribution of patients submitted to PRK and LASIK according to gender.

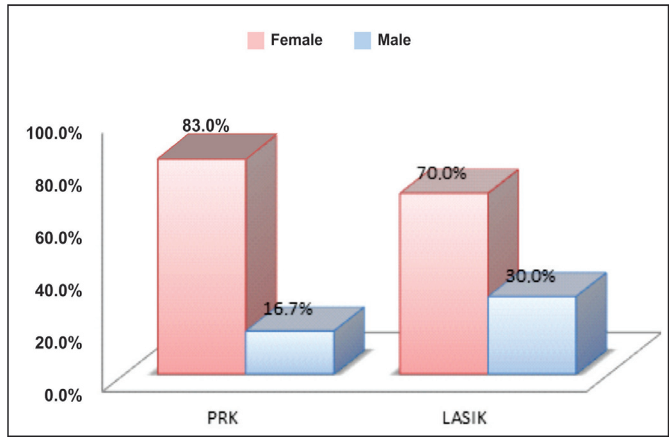
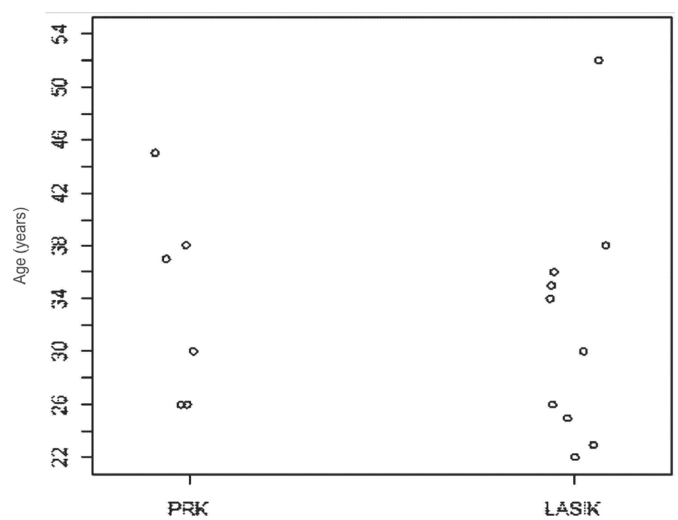


Chart 2

One-dimensional scatter plot for the age (years) of patients submitted to PRK and LASIK.



The TFBU results for all patients combined were13.2 ± 3.3 preoperatively, 11.3 ± 4.4 at 15 PO, and 10.4 ± 3.2 at 30 PO.Statistically-significant differences were found between Pre and 15 PO (p = 0.025) and between Pre and 30 PO (p = 0.001), but not between 15 PO and 30 PO(p = 0.219).The results of the lissamine green test were1.0 ± 0.9 preoperatively, 1.3 ± 1.0 at 15 PO, and 1.0 ± 1.0 at 30 PO.Statistically-significant differences were found between Pre and 15 PO (p = 0.021) and between 15 PO and 30 PO (p = 0.010), but not between Pre and 30 PO(p = 0.768).Finally, the results of the Schirmer testwere17.6 ± 10.6 preoperatively, 14.5 ± 10.8 at 15 PO, and 16.2 ± 11.0 at 30 PO; there were no statistically-significant differences between the three time points (p = 0.107) (Table 2).

Table 2

Mean values and standard deviation of the results ofTFBU (seconds), lissamine green (score) and basal Schirmer test (millimetres).

	Time	Mean ± Standard deviation	Range	p - Value[c]	p-Value[d]
TRFL	pre	13.2 ± 3.3	8,0 – 18.0		0.025*
	15 PO	11.3 ± 4.4	4,0 – 20.0	0.003	0.219**
	30 PO	10.4 ± 3.2	6,0 – 16.0		0.001***
Lissamine	pre	1.0 ± 0.9	0,0 – 3.0	0.019	0.021*
	15 PO	1.3 ± 1.0	0,0 – 3.0		0.010**
	30 PO	1.0 ± 1.0	0,0 – 3.0		0.768***
Schirmer	pre	17.6 ± 10.6	0,0 – 35.0	0.107	-
	15 PO	14.5 ± 10.8	0,0 – 35.0		-
	30 PO	16.2 ± 11.0	0,0 – 35.0		-

[c]ANOVA with blocks, [d]Multiple comparisons using the LSD method
*Comparison between Pre and 15 PO; **Comparison between 15 PO and 30 PO; ***Comparison between Pre and 30 PO.

Table 3

Means and standard deviationsfor the results of TFBU (seconds), lissamine green (score) and basal Schirmertest (millimetres).

Test	Teme	PRK	LASIK	p-Value
TRFL	pre	12.7 ± 2.8	13.4 ± 3.5	0.744[c]
	15 PO	10.5 ± 3.1	11.8 ± 5.1	
	30 PO	10.8 ± 3.0	10.2 ± 3.4	
Lissamine	pre	1.5 ± 0.9	0.8 ± 0.9	0.093[c]
	15 PO	1.7 ± 0.9	1.1 ± 1.0	
	30 PO	1.4 ± 1.1	0.8 ± 0.9	
Schirmer	pre	15.9 ± 10.4	18.6 ± 10.9	0.394[c]
	15º PO	11.9 ± 7.1	16.1 ± 12.5	
	30 PO	13.8 ± 6.9	17.7 ± 12.9	

[c]p-value for the comparison between PRK and LASIK using ANOVA with repeated measures.

Chart 3

Mean individual profiles for the results of TFBU (seconds)in patients submitted to PRK and LASIK.

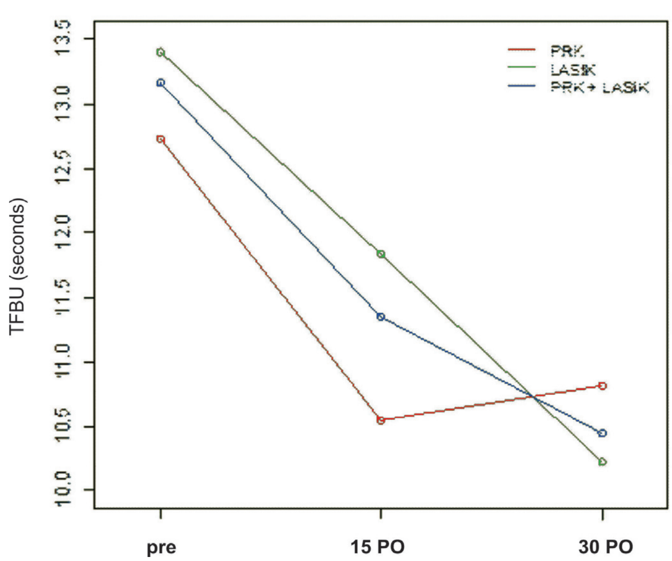


Chart 4

Mean individual profiles for the results of the lissamine green test (score) in patients submitted to PRK and LASIK.

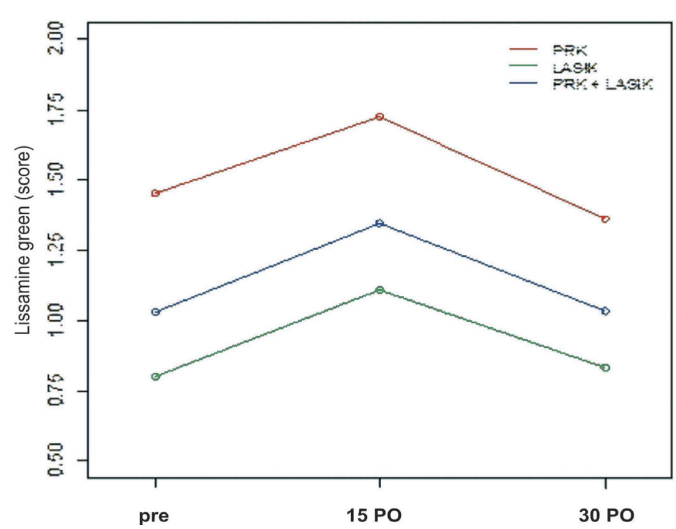
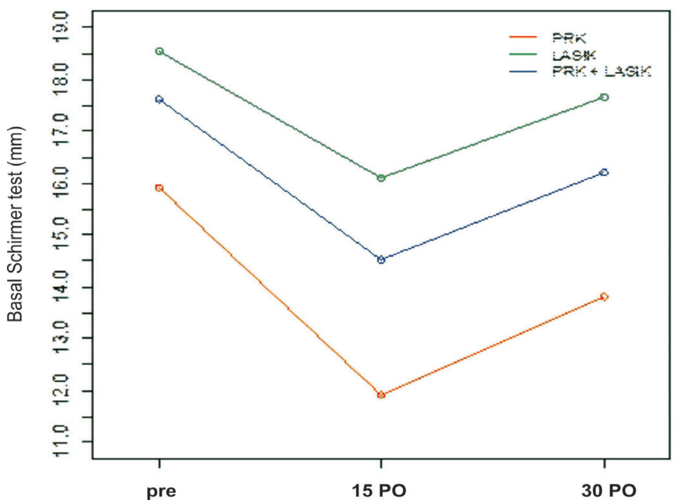


Chart 5

Mean individual profiles for the results of the basal Schirmer test (millimetres) in patients submitted to PRK and LASIK.



When the two groups (PRK and LASIK) were analysed separately, the following results were found:in the TFBU test, the values at Pre, 15 PO and 30 PO, respectively, were12.7 ± 2.8, 10.5 ± 3.1, and 10.8 ± 3.0 for the PRK group, and13.4 ± 3.5, 11.8 ± 5.1, and 10.2 ± 3.4 for the LASIK group. There were no statistically-significant differences between groups (p = 0.744).In the lissamine green test, the values at Pre, 15 PO, and 30 PO were1.5 ± 0.9; 1.7 ± 0.9 1.4 ± 1.1 for the PRK group, and0.8 ± 0.9, 1.1 ± 1.0, and 0.8 ± 0.9 for the LASIK group.Again, there were no significant differencesbetween groups (p = 0.093).In the basal Schirmer test, the values at Pre, 15 PO and 30 PO were15.9 ± 10.4, 11.9 ± 7.1, and 13.8 ± 6.9 for the PRK group, and18.6 ± 10.9, 16.1 ± 12.5, and 17.7 ± 12.9 for the LASIK group.Once again, there were no statistically-significant differences between groups (p = 0.394) (Table 3).

Discussion

Regarding the sample population of this study, it is important to stress that there were no statistically-significant differences between groups (PRK and LASIK)regarding age or gender (Table 1, Charts 1 and 2) which could influence the incidence of dry eye in each group.Older patients and women are more likely to develop dry eye.[6]

When all patients were grouped together, there was a statistically-significant reduction inTFBU values at 15 POin relation to preoperative values, and at 30 PO the values had decreased a little more (but with no significant difference compared to 15 PO) (Table 2, Chart 3).This is consistent with some studies in the literature which found a decrease in TFBU.[7,8] TFBU is an important test to assess the stability of the tear film, and together with the evaluation of symptoms, it is considered the most reliable test for dry eye syndrome because it is more reproducible, i.e. it shows less variation between two tests.[9]Thus, this study confirms that patients undergoing refractive surgery have a tendency to develop dry eye.

In the lissamine green test, a significant increase was found at 15 POcompared to the preoperative period, followed by a significant decrease at 30 PO, reaching a score statistically similar to preoperative values (Table 2, Chart 4).Lissamine green is an important dye thatstains damagedcells in the conjunctival and corneal epithelium, which can be found in patients with lacrimal film deficiency.Its action is similar to rose bengaldye, but it causes less irritation.The lissamine green test is moderately reproducible.[9]Itshowed that epithelial cells were actually damaged in the first two postoperativeweeks regardless of the surgical technique, with scores returning to normal within a month after surgery.Such damage may have been caused by the procedure itself or may be a consequence of dry eye.

In the basal Schirmer test, no statistically-significant differenceswere found between the three time points (Pre, 15 PO, and 30 PO) (Table 3, Chart 5), in contrast with several other studies.[1,7,8]As can be seen in the chart, Schirmer test values tended to decrease postoperatively, but the reduction was not statistically significant.It should be noted that most previous studies used the type 1Schirmer test (without instillation of anaesthetic eye drops) following refractive surgery instead of the basal Schirmer test used in ourstudy (where anaesthetic eye drops were instilled in conjunctival sac before placing the Schirmer strip).The type 1 Schirmer test is probably more affected after refractive surgery, as it assesses both basal and reflex tear secretion, while the basal Schirmer test assesses basal secretion only.However, Nichols et al.[9]showed that the type 1 Schirmer test has poor reproducibility in patients with mild to moderate dry eye, being more reliable only in patients with severe dry eye.This is why we elected to use the basal Schirmer test in this study.Moreover, the preoperativeevaluation of patients included an assessment of static refraction with anaesthetic, cycloplegic, and tropicamide eye drops on the same day as the dry eye tests were conducted;therefore, the basal Schirmer test was also preferred to avoid any bias that could have been caused by the residual influence of those drugs.

It should also be noted that even though all tests were conducted in the same environment in a closed room, there were variations in temperature and humidity in the city of São Paulo, where the experiment was conducted, which could certainly have influenced results.

Some studies show that patients submitted LASIK have a higher incidence and a longer duration of dry eye than those undergoing PRK[7,8].In our study, however, neither technique was superior to the other in the three time points (Pre, 15 PO and 30 PO) (Table 3).This may be related to the fact that other studies used a microkeratome, instead of femtosecond laser, to create the corneal flap.The introduction of femtosecond laser in LASIK has created the prospect to reduce the incidence of dry eye, as it is a safer and more accurate method than the microkeratome.[4,5]Salomão et al.[10] found that patients submitted to LASIK whose corneal flap had been created using the femtosecond laser showed less dry eye than those whose flap had beencreated with a manual microkeratome.In contrast, Golas et al.[6]found no statistically-significant differences between these two groups as regards dry eye symptoms.

It is therefore important to stress the need to observe patients closely for the development of dry eye after surgery.Furthermore, according to our results, there were no significant differences between both surgical techniques as regards changes in the tear film.

Conclusion

The present study foundchanges in the tear film of patients submitted to PRK and LASIK with femtosecond laser; in particular, changes were observed in the TFBU and lissamine green tests, with the latter returning to preoperative values within a month after surgery.No significant changes were found in the Schirmer test within the first postoperative month.PRK and LASIK with femtosecond laser produced similar changes to the tear film.

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