The Effect of Topical Apraclonidine on Subconjunctival Hemorrhage and Flap Adherence in LASIK Patients

Ioannis M. Aslanides, MD, PhD; Nikolaos S. Tsiklis, MD; Efekan Ozkilic, MD; Efekan Coskunseven, MD; Ioannis G. Pallikaris, MD, PhD; Mirko R. Jankov, MD

ABSTRACT

PURPOSE: To determine whether the use of topical apraclonidine just before the LASIK procedure prevents subconjunctival hemorrhage and to study its effect on postoperative flap adherence.

METHODS: Topical apraclonidine 0.125% was randomly applied to 1 eye of 66 myopic patients who underwent primary bilateral LASIK. Apraclonidine was instilled 1 hour prior to and 30 seconds before placing the vacuum ring of the microkeratome, whereas the other eye served as control. Thirty minutes after the operation, all patients were examined by the surgeon to evaluate hyperemia and identify flap-related complications (eg, slippage, dislocation, or flap folds). The size of subconjunctival hemorrhage was also evaluated on postoperative days 1 and 7. All 132 eyes in the study were examined after surgery to identify flap folds and/or their dislocation.

RESULTS: In the apraclonidine group, 48 (72.8%) eyes had no hyperemia, 16 (24.2%) eyes had mild hyperemia, 2 (3%) eyes had moderate hyperemia, and no (0%) eyes had severe hyperemia. In the control group, 37 (56.1%) eyes had mild hyperemia, 21 (31.8%) eyes had moderate hyperemia, 1 (1.5%) eye had severe hyperemia, and 7 (10.6%) eyes had no hyperemia. In the apraclonidine group, 44 (66.7%) eyes had no subconjunctival hemorrhage (grade 0); grade 1 was present in 19 (28.8%) eyes whereas grades 2 and 3 were present in 2 (3%) eyes and 1 (1.5%) eye, respectively. In the control group, 19 (28.8%) eyes showed grade 0, 13 (19.7%) eyes had grade 1, and grades 2 and 3 were present in 20 (30.3%) eyes and 14 (21.2%) eyes, respectively. Chi-square test showed a highly significant difference between the two groups ($P<.001$). No flap-related problems were reported in either group.

CONCLUSIONS: Topical apraclonidine applied before LASIK surgery may prevent immediate postoperative hyperemia and prolonged subconjunctival hemorrhage by its alpha-mimetic vasoconstrictor effect without inducing flap adherence complication. [*J Refract Surg*. 2006;22:585-588.]

Laser in situ keratomileusis (LASIK) is a popular and relatively safe surgical procedure for the correction of myopia, hyperopia, and astigmatism.[1] Although medical reasons are involved, many patients who seek LASIK surgery would like to free themselves from their glasses or contact lenses due to practical or cosmetic reasons. Thus, they want to see well from the first postoperative day. However, a number of patients have postoperative hyperemia and subconjunctival hemorrhage[2-4] due to surgical manipulation, mainly because of the use of a vacuum ring during flap creation. Although postoperative subconjunctival hemorrhage is considered a temporary cosmetic problem, a significant degree of unnecessary anxiety and false alarm may arise in some patients in the immediate postoperative days.

Apart from its well-described function among anti-glaucoma drugs,[5] topical apraclonidine applied just before LASIK surgery may cause vasoconstriction[5] of conjunctival vessels and thus reduce the occurrence and severity of subconjunctival hemorrhage, as described with another vasoconstrictor, brominidine.[6,7]

Proper adhesion between the corneal flap and stromal bed is mandatory after LASIK surgery to properly restore the corneal integrity, promote normal healing, and establish an adequate refractive outcome. Several flap complications that occur from poor flap adherence have been described,[2,3] and there is controversial evidence that use of the vasoconstrictor brimonidine may increase the incidence of such complications.[7]

The aim of this study is to analyze the effectiveness of topical apraclonidine on decreasing conjunctival hyperemia and subconjunctival hemorrhage and its potential influence on flap adherence after LASIK surgery.

From VEIC - Vardinoyiannion Eye Institute of Crete, University of Crete, Greece (Aslanides, Tsiklis, Pallikaris, Jankov); World Eye Hospital, Istanbul, Turkey (Ozkilic, Coskunseven); and Instituto de Visão, Escola Paulista de Medicina, Universidade Federal de São Paulo, Brazil (Jankov).

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Correspondence: Ioannis M. Aslanides, MD, PhD, VEIC - Vardinoyiannion Eye Institute of Crete, University of Crete, PO Box 2208, 71003 Voutes, Heraklion Crete, Greece. Fax: 30 2810 394 653; E-mail: aslanides@med.uoc.gr or visioncare@mac.com

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PATIENTS AND METHODS

Sixty-six consecutive patients (32 men and 34 women, 132 eyes) who underwent primary bilateral LASIK in June 2004 for their refractive errors (myopia, astigmatism, and hyperopia) were included in this study. Mean spherical equivalent refraction was -6.43 ± 2.03 diopters (D) (range: -2.38 to -10.63 D). Mean patient age was 33 ± 11 years (range: 18 to 62 years).

All procedures were performed by the same surgeon (I.M.A.), using an identical technique in all eyes regarding preoperative medication, use of microkeratome, flap manipulation, and drying time. The details of the technique are as follows: one drop of proparacaine 0.5% (Alcaine; Alcon, Ft Worth, Tex) was instilled into each eye and the upper and lower lids were cleaned with povidone-iodine (Betadine; Lavipharm Hellas AE, Athens, Greece). One additional drop of proparacaine was added to the operative eye immediately prior to the procedure. A drape was used to retract the eyelashes, and a speculum was placed into the operative eye, while the fellow eye was occluded with an eye shield. Methylene blue (Visimark; Becton Dickinson & Co, Franklin Lakes, NJ) was used to mark the cornea in preparation for making the lamellar flap. A Moria M2 microkeratome (Moria Surgical, Antony, France) was used in manual mode to make a superiorly hinged flap in all 132 eyes. After the flap was made, the conjunctival fornix was dried using a surgical sponge (Murocel; Medtronic Solan, Jacksonville, Fla). The flap was retracted back using a double-barrelled LASIK cannula (Moria Surgical). After laser ablation with the Allegretto Wave excimer laser (WaveLight Laser Technologie AG, Erlangen, Germany), the flap was floated back into position with minimal irrigation of balanced salt solution (BSS, Alcon) using the aforementioned cannula. A dry Murocel sponge was then used to absorb the excess moisture from beneath the flap, dry the periphery of the flap, and ensure a symmetric flap gutter. Subsequently, a wet sponge was used to smooth the flap and ensure its proper alignment with no visible folds. All flaps were allowed to dry for 1.5 minutes. The symmetry of the gutter was further evaluated by instilling a chalk white drop of prednisolone acetate (Pred Forte; Allergan Pharmaceuticals Ltd, Westport, County Mayo, Ireland), which clearly demarcated the exact outline of the gutter. A striae test was performed to ensure proper flap adherence by pressing the cornea just outside of the flap edge with a Murocel sponge to check whether striae outside the flap were in continuation with those inside the flap. All eyes were examined within 15 minutes after surgery. Patients were instructed to keep their eyes lightly closed, to wear protective eye shields at night, and return the following day for re-examination.

In addition to the previously described standard technique, a drop of 0.125% topical apraclonidine (Iopidine; Alcon-Couvreur NV, Puurs, Belgium) was applied randomly (with a flip of a coin) to one eye of each patient 1 hour prior to and 30 seconds before placing the vacuum ring of the microkeratome. In the control eye, a drop of sodium hyaluronate 0.18% (Vismed; TRB Chemedica AG, Haar/Munchen, Germany) was instilled.

Thirty minutes postoperatively, severity of hyperemia of both eyes was detected by an independent observer (N.S.T.) in a double-blind manner and classified as follows: grade 0, no hyperemia; grade 1, mild; grade 2, moderate, and grade 3, severe. The size of subconjunctival hemorrhage was detected on the first postoperative day. The size of the subconjunctival hemorrhage was classified by slit-lamp examination as follows: grade 0, no hemorrhage present; grade 1, <1 mm (micro-hemorrhage); grade 2, between 1 and 3 mm (moderate hemorrhage); and grade 3, >3 mm (macro-hemorrhage).

The appearance of the flap with respect to folds and dislocations was carefully monitored using slit-lamp microscopy immediately after (<15 minutes) and on the day after the surgery (24 hours). Folds were defined as a series of parallel ridges in the flap that were best seen with retro-illumination and stained negatively with fluorescein. A dislocation was defined as folds accompanied by ≥ 0.5-mm displacement of the flap edge from the edge of the lamellar cut.

Postoperatively, patients were prescribed sodium flurbiprofen 0.03% (Ocuflur, Allergan) drops 4 times a day for 2 days, dexamethasone 0.1% and tobramycin 0.3% (Tobradex, Alcon) drops 4 times a day for 2 weeks, and Vismed drops initially hourly and then when necessary for 1 month thereafter.

Statistical analysis was performed using a chi-square test, and $P<.01$ was considered statistically significant. For this statistical test, the expected frequency could not be <5 in $>20\%$ of cells,[8] therefore the values for moderate and severe hyperemia were combined for the purpose of statistical evaluation.

RESULTS

Vasoconstrictive Effects

In the apraclonidine group, 48 (72.8%) eyes had no hyperemia, 16 (24.2%) eyes had mild hyperemia, and 2 eyes (3%) had moderate hyperemia. No eye had severe hyperemia. In the control group, 37 (56.1%) eyes had mild, 21 (31.8%) eyes moderate, and 1 (1.5%) eye had severe hyperemia. Seven (10.6%) eyes did not have any hyperemia (Fig 1). Chi-square test revealed a significant difference between the two groups ($P<.001$).

Concerning the subconjunctival hemorrhage, in the

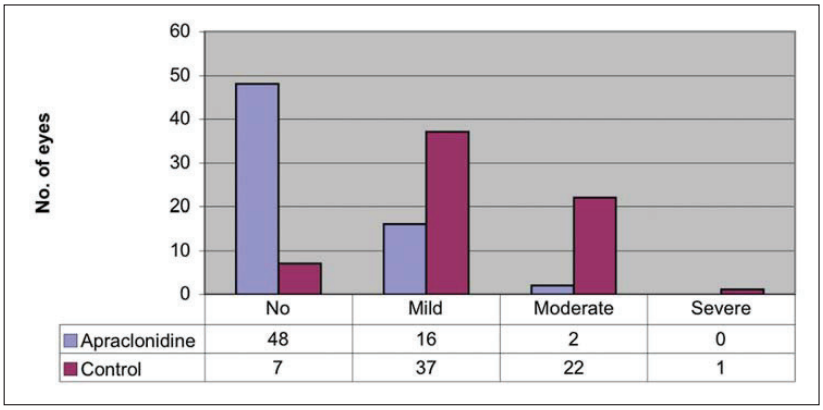

Figure 1. Conjunctival hyperemia in eyes with apraclonidine versus control.

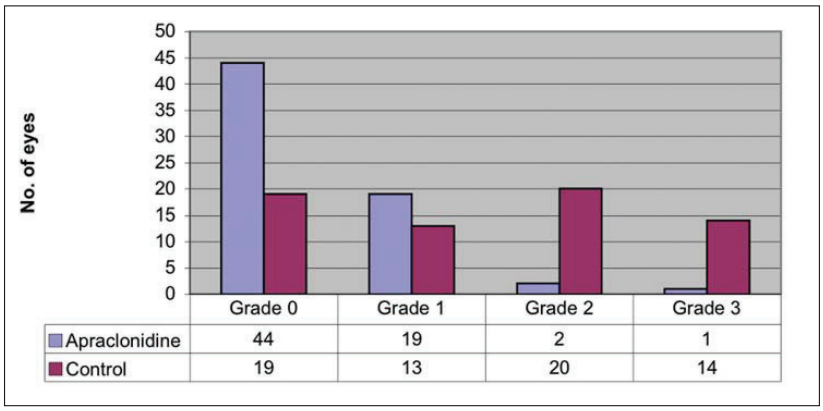

Figure 2. Subconjunctival hemorrhage in eyes with apraclonidine versus control.

apraclonidine group, 44 (66.7%) eyes had no subconjunctival hemorrhage (grade 0), and grade 1 was present in 19 (28.8%) eyes, whereas grades 2 and 3 were present in 2 (3%) eyes and 1 (1.5%) eye, respectively. In the control group, 19 (28.8%) eyes were grade 0, 13 (19.7%) eyes were grade, and grades 2 and 3 were present in 20 (30.3%) eyes and 14 (21.2%) eyes, respectively (Fig 2). A significant difference was noted between the two groups using the chi-square test ($P<.001$).

Flap Adherence and Other Effects

No eye had any flap complications in the postoperative course, including flap adherence problems. All eyes in the apraclonidine group had a slight upper eyelid retraction, which was not present the following day.

DISCUSSION

Although LASIK is sometimes performed for medical reasons (eg, correction of anisometropia), it is performed mostly for cosmetic purposes. After LASIK surgery, most patients experience subconjunctival hemorrhage due to surgical manipulation and the use of the vacuum ring during flap creation. Because it is a self-limited and temporary complication, most surgeons do not consider subconjunctival hemorrhage a problem. Many patients, however, despite prior counseling, perceive this as an untoward effect rather than just a cosmetic problem. Patients may be alarmed and worried about the surgical outcome, although it usually resolves spontaneously within 2 to 3 weeks; this condition may persist even longer in some cases.

Topical apraclonidine has a vasoconstrictive[5] effect due to its alpha-mimetic action and is used for glaucoma treatment. Vajpayee et al[9] determined that interface hemorrhage during LASIK surgery may affect visual performance. Topical apraclonidine may prevent interface hemorrhage and therefore prevent its possible deteriorative effect on postoperative course and visual outcome. Before LASIK, instillation of one drop of apraclonidine may prevent hyperemia and subconjunctival hemorrhage by its vasoconstrictive effect on conjunctival vessels.

Topical apraclonidine also has an ocular hypotensive effect and is used in glaucoma treatment as 0.125% to 0.5% drops due to its partial agonistic effect on alpha-2 adrenergic receptors.

As more speculations arise from glaucoma special-

ists about potential barotrauma damage on the optic nerve head during suction in LASIK surgery, apraclonidine might be an additional protection factor in our everyday surgical routine. Because the perfusion pressure equals the systemic blood pressure minus the intraocular pressure (IOP), when apraclonidine is applied just 30 seconds before LASIK surgery, its vasoconstrictive effect begins prior to vacuum ring application. However, as its antiglaucomatous effect does not take place until 1 hour later with the peak at 3 to 5 hours,[5] one drop was also applied 1 hour prior to the surgery. This has another potentially beneficial effect on the eye, as it may decrease the risk of posttraumatic IOP peak (barotrauma) after the surgery. McCarty et al,[10] on the other hand, found that the use of brimonidine prior to LASIK did not affect the structure or function of the optic nerve, and that the alteration in corneal birefringence after excimer laser ablation may explain the reduction in direct retinal nerve fiber layer measures without the concomitant change in ratio measures. However, as this surpasses the scope of our study, we suggest further clinical studies focusing on the numerous variables involved in the optic nerve head perfusion be carried out to clarify this hypothesis.

Norden[6] conducted a double-masked study and concluded that topical brimonidine before LASIK surgery may decrease the amount of subconjunctival hemorrhage and hyperemia due to LASIK surgery. Our study confirms the hypothesis that alpha-agonists applied topically, in our case apraclonidine, may significantly decrease hyperemia and subconjunctival hemorrhage after LASIK surgery.

In all cases, eyes treated with apraclonidine had upper lid retraction in the early postoperative period due to stimulation of the upper lid Muller muscle by the alpha-mimetic action of apraclonidine. Left eyes in which apraclonidine was applied had upper lid retraction and less hyperemia; however, right eyes without apraclonidine had relatively ptotic and more hyperemic appearance. The difference in appearance revealed significant cosmetic disparity between the two eyes.

Topical apraclonidine may lead to ocular and dermatologic allergic reactions[5] in chronic use as in glaucoma treatment. Therefore, it should not be used for a long period of time to prevent hyperemia, otherwise rebound effect may occur.[5] In this study, we did not detect any allergic reaction due to topical apraclonidine. This may be due to the single use of the drug.

Walter and Gilbert[7] concluded that topical brimonidine application before LASIK surgery may lead to an increase in abnormal flap adhesion. Their conclusion was based on a retrospective non-controlled study of 39 eyes, which we believe is an inadequate study type and too small a number of eyes for such a conclusion. In our prospective, randomized, controlled study with three times the number of eyes, no flap adhesion complications occurred in the eyes that received apraclonidine.

There are several hypotheses regarding the topical influence of alpha-2 agonistic effect, such as a direct lubricant impact, a desiccation or ischemic effect of the anterior segment due to anterior ocular vessels constriction, and/or direct toxic effect to the endothelial cells.[7] However, we tend to agree with Norden[6] that a simpler reason, such as excess moisture on the bed and insufficient flap stroking, may be responsible for the poor flap adherence described previously.

Topical apraclonidine before LASIK surgery may prevent early postoperative hyperemia and subconjunctival hemorrhage without adverse effects on the flap adherence.

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