

A randomized, comparative study of fluorometholone 0.2% and fluorometholone 0.1% acetate after photorefractive keratectomy

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PURPOSE. To compare the efficacy and tolerance of fluorometholone 0.1% acetate and fluorometholone 0.2% eyedrops in the postoperative management of photorefractive keratectomy (PRK).

METHODS. A randomised single-blind comparative study was performed on two groups of 30 patients who underwent myopic PRK. The first group was given fluorometholone 0.1% acetate and the second fluorometholone 0.2%. Uncorrected and best corrected visual acuity, haze, IOP and local tolerance were evaluated. Statistical analysis was done using parametric and non-parametric tests.

RESULTS. Visual acuity did not differ in the two groups; both were homogeneous as far as refractive error and haze were concerned. Three patients (10%) treated with fluorometholone 0.2% and two patients (6.6%) with fluorometholone 0.1% acetate developed ocular hypertension, but this was not statistically significant.

CONCLUSIONS. Fluorometholone 0.1% acetate was effective on inflammation after PRK, with the same efficacy as fluorometholone 0.2%. (*Eur J Ophthalmol* 2000; 10: 39-45)

KEY WORDS: Fluorometholone acetate, PRK, Flying spot excimer laser, Haze, Intraocular pressure, Visual acuity

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INTRODUCTION

Excimer laser photorefractive keratectomy (PRK) has become the most commonly used method of refractive surgery in the world, thanks to the predictability of the results and the minimal structural changes induced in corneal tissue (1). The anatomical and functional success of this method are also due to post-operative stromal modulation through topical corticosteroids, whose use was already proposed by Seiler, decreasing in frequency, from 4 up to 6 months (2).

A large number of studies have shown the importance of corticosteroids in post-operative therapy: these patients complain of a lower incidence of haze and

regression (3-5). However, prolonged use of these drugs causes problems from the point of view of side effects and compliance. One of the most frequent complications was ocular hypertension, reported by several authors (6-9), and its incidence varies with the molecule employed. Steroid-induced ocular hypertension may regress when therapy is discontinued or can be controlled by administering β blockers (10).

Thus, two different postoperative strategies are possible: to administer highly effective molecules with minimal side effects (e.g. clobetasone, fluorometholone) or to prescribe non-steroidal antiinflammatory drugs (NSAIDs). The literature on the subject shows that NSAIDs seem to be effective but only in cases with myopia

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FML 0.2% vs FML 0.1% acetate after PRK

not exceeding 6D (10-12).

Previous studies investigated whether other classes of drugs might play a clinical role in the postoperative management of haze, and mytomicin C and cyclosporin proved effective, but their side effects were considerable (13-15).

Finally, some authors recommend "no drug" therapy: they give their patients no medicines at all, and their refractive outcomes are similar to patients given the various drugs (16-18).

In our study, we evaluated the clinical efficacy of fluorometholone 0.1% acetate in comparison with fluorometholone 0.2%, in a group of patients who underwent PRK.

METHODS

We compared the clinical efficacy of fluoro-metholone (FML) 0.1% acetate and FML 0.2% ophthalmic suspensions. This comparative, randomized single-blind study was carried out on patients undergoing excimer laser surgery for myopia. The study lasted six months.

Selection of patients

Between February and June 1998, 72 consecutive patients requested excimer laser surgery for myopia at the Department of Ophthalmology, University of Bari, Italy. After giving informed consent to the study, each patient underwent a preoperative clinical examination. Detailed ocular and general medical history were collected. All visits were done by the same physician (M.V.), and included slit-lamp examination, cycloplegic refraction using an autorefractometer, uncorrected and best spectacle-corrected visual acuity, reported on the ETDRS chart, altimetric corneal topography with pupillometry (Orbscan, Orbtex, Salt Lake City, Utah). We admitted patients aged from 21 to 40 years, with stable refraction for at least two years, attempted myopic correction between -1.5 and -8.0 diopters (D) and astigmatism, if present, ranging from 0.5 to 2.5 D, best-corrected visual acuity better than 20/32, no prior ocular surgery or glaucoma treatment. Exclusion criteria were unilateral amblyopia (one patient), evidence of ocular disorders (infectious, inflammatory, degenerative) in the patient's medical history (four patients with keratoconus, two with keratoconjunc-

tivitis sicca), steroid therapy within the past 30 days or NSAID within the past 14 days (three patients), intolerance of one of the components of the study drug (one patient), and ocular hypertension, i.e. untreated IOP greater than 22 mmHg with normal-appearing optic nerves and visual field (one patient). Sixty patients (60 eyes) met all the selection criteria and entered the study.

Patients were randomly divided into two groups: 30 (30 eyes) were assigned to FML 0.2%, and received 0.2% FML, and 30 (30 eyes) to the FML acetate group, treated with 0.1% FML acetate. The randomization code was computer-generated and all assignments were done by the same physician (A.M.).

Surgical procedure

All surgical procedures were performed by the same surgeon (M.V.), using a Laserscan 2000 (Lasersight, Orlando, FL), which reprofiles the corneal surface by means of a galvanometric scanning delivery system (flying spot). Its technical features were: repetition rate 100 Hz, fluence 160 mJ/cm², beam diameter 1 mm. The laser ablation algorithm allowed the operator to perform corneal ablations using a single-pass multi-zone technique: the number of zones and their minimal and maximum diameter were computed by integrating preoperative mesopic pupillometric measurements and corneal curvature with the depth of the corneal ablation zone. Further safety devices were the active eye-tracker, which automatically centered the ablation over the pupil, and the internal power stabilizer, which ensured uniform delivery of energy throughout the treatment.

Our surgical procedure provides a single zone PRK with a wide ablation profile (up to 7 mm) for low myopia (less than -3.00 D), whereas for moderate and severe myopia two to four zones were used, with a slightly narrower profile (from 5 to 6.7 mm), in order to obtain ablation zones not deeper than 100 µm.

After administration of a topical anesthetic drop (0.4% oxybuprocaine hydrochloride, Novesina, Sandoz, Italy), the laser ablation was performed with the patient being asked to fixate a blinking green target light within the laser aperture, then the eye tracker was switched on. The epithelium within the ablation zone was removed with a blunt Desmarres blade. On completion of the

surgical treatment, all patients received one drop of FML 0.1% acetate (Flarex, Alcon, Milano, Italy), ofloxacin (Exocin, Allergan, Roma, Italy) and 0.03% flurbiprofen preservative-free ophthalmic solution (Ocufen 40, Allergan, Roma, Italy). A soft contact lens (Acuvue, Johnson and Johnson, Jacksonville, FL) was applied. In addition, all patients were advised to take additional analgesic tablets (ketorolac tromethamine, Lixidol, 10 mg tablets, Farmitalia, Milano, Italy) if the pain did not disappear after topical therapy. Eyedrops were administered four times a day until re-epithelialization occurred.

After this first postoperative phase, the soft contact lenses were removed and each unlabelled container was numbered according to the code and then given to the patient. Both drugs (0.2% FML and 0.1% FML acetate) were dispensed four times a day for one month and thereafter with decreasing frequency every three weeks. If the patient complained of ocular dryness or discomfort, artificial tears were administered.

Post-operative evaluation

Post-operative examinations were repeated every 24 hours until re-epithelialization occurred, and then after 15, 30, 60, 90, and 180 days. Post-re-epithelialization visits included slit-lamp examination with corneal haze assessment (on a scale of 0 to 4) (19), evaluation of uncorrected and best-corrected visual acuity and manifest and cycloplegic refraction, corneal altimetric topography and measurement of intraocular pressure (IOP), routinely done by two physicians (M.V., G.M.Q.). Subjective symptoms and objective findings related to the eyedrops were evaluated (burning sensation, conjunctival edema, etc.) and the difference between attempted and achieved myopic correction was calculated. At the end of each postoperative visit, patients gave their opinion of eye-drop tolerance on a subjective scale: good, medium or acceptable.

On completion of the steroid treatment, all patients were asked whether they were able to identify which group they belonged to. Negative answers were considered an indicator of successful masking. The therapeutic protocol was completed within four months and the allocation code was broken only after completion of the statistical analysis.

Statistical analysis

The sample distribution analysis was carried out using the Kolmogorov-Smirnov test; this confirmed the accuracy of the parametric and non-parametric tests. All means were arithmetical. Homogeneity between the groups was evaluated using Student's t-test at baseline. Visual acuity and IOP were analysed using the paired t-test at baseline (after evaluation of homogeneity) and, postoperatively, by two-way ANOVA. Significant probabilities involving "time" were studied with Tukey's multiple comparison test. The chi-square test and Newman-Keuls test were used to evaluate haze and ocular tolerance.

Since all patients were examined at each time-point, the data can be considered complete. SPSS, JMP (SAS Institute) and StatSoft statistical packages were used. Differences were considered statistically significant for probabilities smaller than 0.05.

RESULTS

Characteristics of patients

The sample distribution according to age and sex did not show any significant difference (Kolmogorov-Smirnov test); 40% of the patients were male (12+12) and 60% female (18+18). Mean age was 31.97 ± 9.44 years (30.17 ± 8.22 in the FML acetate group, and 33.27 ± 10.43 in the FML 0.2% group). No significant difference was shown between the groups.

Uncorrected visual acuity

Visual acuity was tested at each time point. At baseline, there were no real differences (t-test: $p=0.721$). ANOVA showed a "time effect" in both groups with a similar improvement in the post-operative period. Uncorrected visual acuity increased from a pre-operative mean of 1.03 ± 0.91 to 0.15 ± 0.6 after 15 days to 0.08 ± 0.76 after 30 days in the FML acetate group, and from 1.08 ± 1.08 to 0.24 ± 0.55 after 15 days to 0.14 ± 0.57 after 30 days in the FML 0.2% group.

These data remained constant at later time points (60, 90 and 180 days) (Fig. 1).

FML 0.2% vs FML 0.1% acetate after PRK

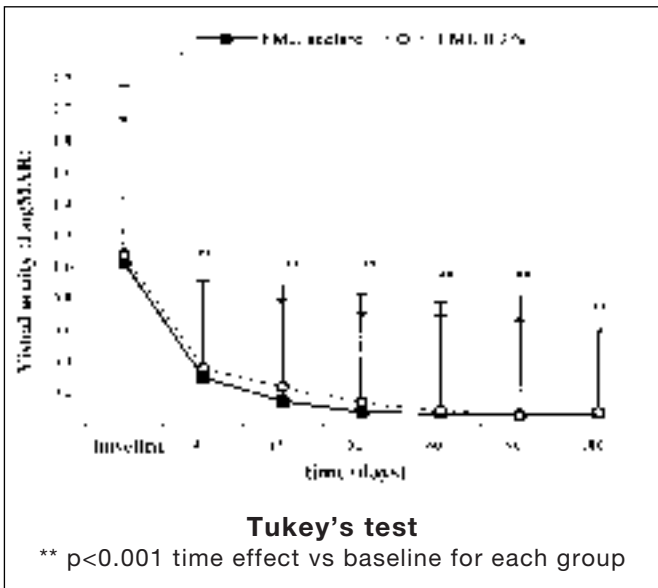


Fig. 1 - Change in uncorrected visual acuity (UCVA) (Log MAR) with time (days).

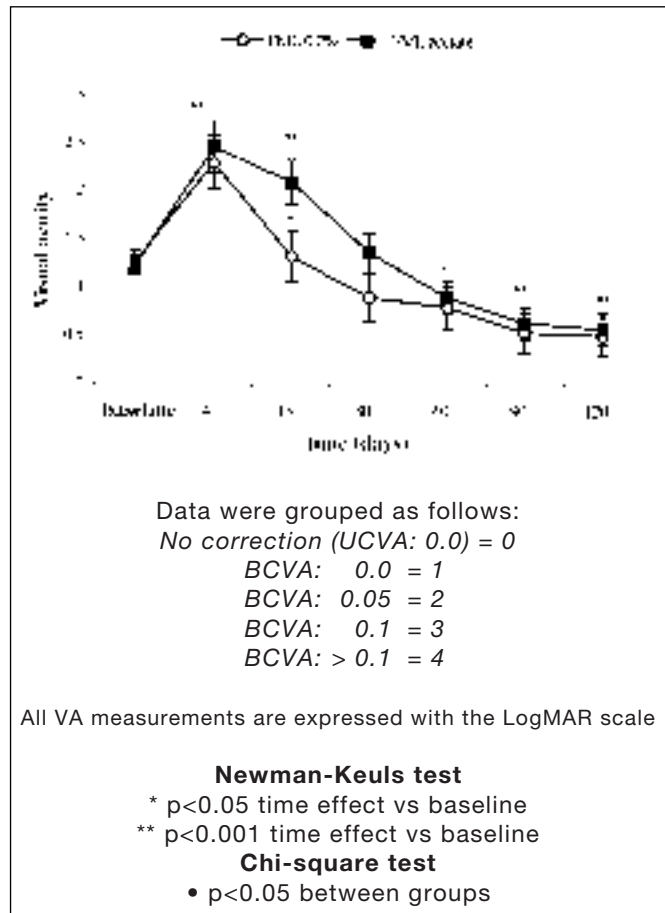


Fig. 2 - Change in best-corrected visual acuity (BCVA) with time (days).

Best spectacle-corrected visual acuity

As shown in Figure 2, no real difference was observed in the two groups except at 15 days (1.33 ± 1.24 in the FML acetate group, 2.10 ± 1.47 in the FML 0.2% group). If we divide patients according to attempted myopic correction, after 180 days best-corrected visual acuity was significantly better in those with myopic correction lower than 6D ($p=0.038$ in FML acetate group, $p=0.05$ in FML 0.2% group), with no significant difference between drugs ($p=0.970$ for myopic corrections lower than 6D, $p=0.600$ for correction over 6D).

Intraocular pressure

IOP was measured by applanation tonometry. Mean values were not different (Fig. 3). Steroid-induced ocular hypertension occurred with no significant difference between groups ($p=1.000$): three patients from the FML 0.2% group (10%) and two patients from the

FML acetate group (6.6%) had post-operative ocular hypertension at 15 and 30 days (FML 0.2% group: 28, 31, 26 mmHg; FML acetate group: 27, 26 mmHg). Beta-blocker eyedrops lowered the IOP so that patients could continue the trial.

Haze

The Newman-Keuls test did not show any significant differences between groups, but only a "time effect" (Fig. 4). Mean haze was lower than 1 in both groups, and increased physiologically at the 60-day and 90-day controls, which correspond to the highest stromal reaction after PRK. Stratifying patients in two groups according to the attempted myopic correction (myopic correction lower than or over 6 diopters), at the 180-day timepoint haze was significantly higher for patients undergoing higher corrections in both groups ($p=0.043$ in the 0.2% FML group and $p=0.049$ in the FML acetate group).

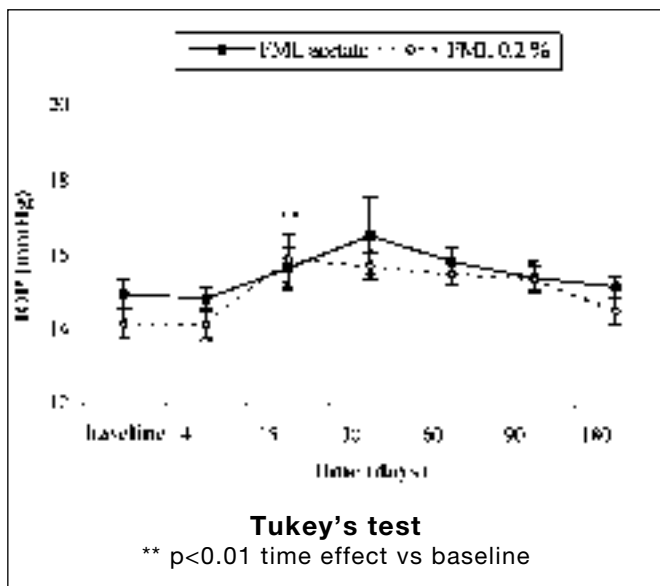


Fig. 3 - Change in IOP (mmHg) with time (180 days).

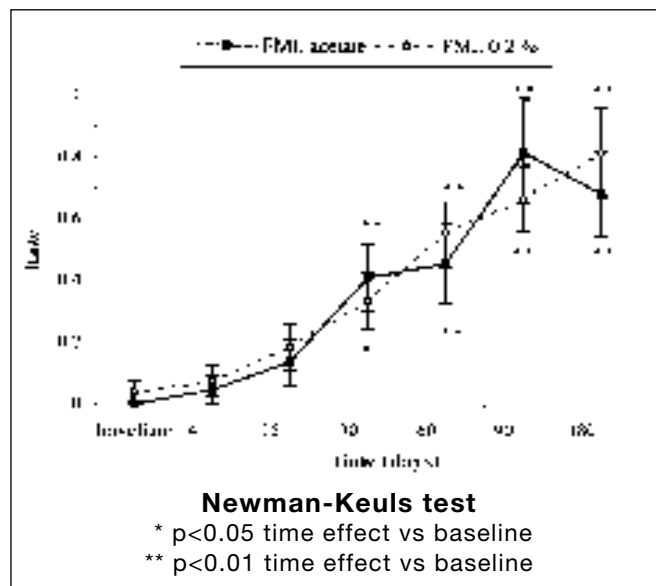


Fig. 4 - Change in corneal haze with time (180 days).

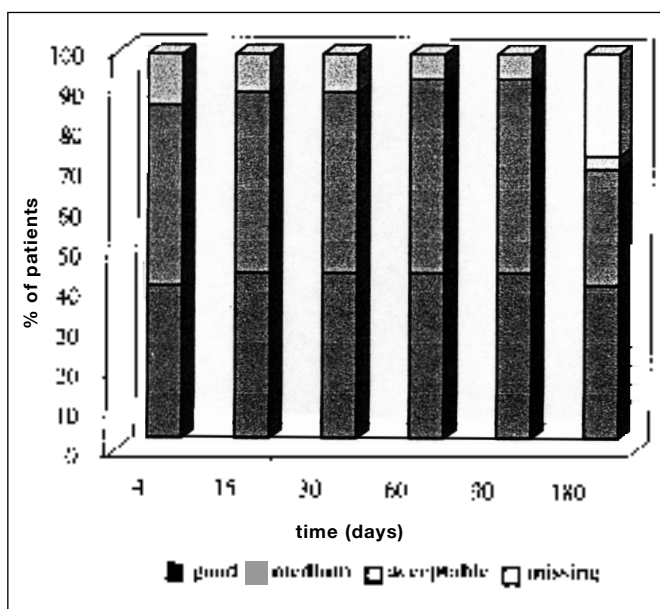


Fig. 5 - Subjective evaluation of tolerance (FML acetate) at different time points.

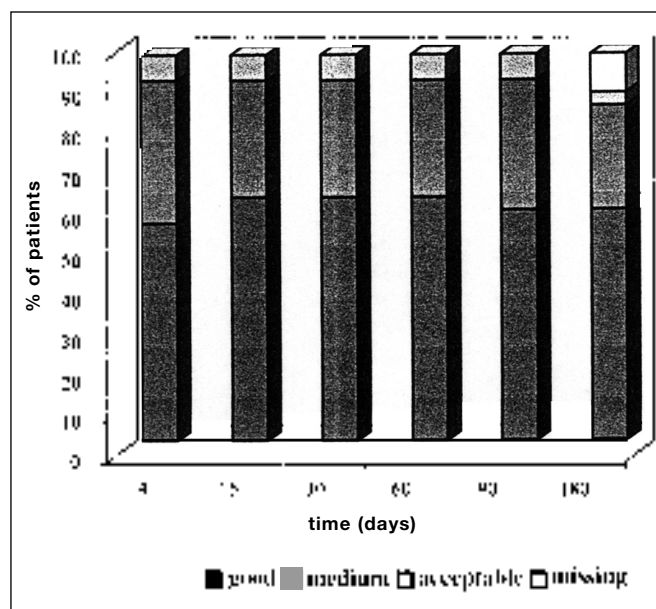


Fig. 6 - Subjective evaluation of tolerance (FML 0.2%) at different time points.

Ocular tolerance

Ocular tolerance was good in both groups (Figs. 5, 6) without any real difference. However, there was a higher incidence of ocular dryness complaints in the FML acetate group, which was promptly resolved by artificial tears.

DISCUSSION

After PRK, corticosteroids control the response of keratocytes, by inhibiting DNA synthesis and consequently the cellular activity related to collagen neosynthesis (20). Prolonged administration of corticosteroid eyedrops has some side effects such as ocular hypertension,

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cataract, fungine infections, and herpetic keratitis (16). All these complications are related to the molecule used and the duration of administration. For this reason we prefer local anti-inflammatory drugs with high anti-inflammatory efficacy and low side effects, such as fluorometholone (21, 22).

The pharmacological properties of this drug have been well studied. McGhee reported a maximal concentration of FML in the aqueous humour (5.1 ng/ml) in comparison with prednisolone acetate 1% (171.4 ng/ml), 60 minutes after administration (23). The different effects on ocular pressure could also be due to the different degrees of penetration into the anterior chamber of several metabolites. For example, FML is metabolised in the aqueous humour to 20- α -dehydro FML which is hardly active at all at the trabecular level, as reported by Akure (24).

Previous studies have shown that the acetate derivative of FML suppresses anterior segment inflammation more effectively than the alcohol base (20, 22), which barely penetrates the anterior chamber. FML acetate also seems to have scant propensity for raising the IOP, like the alcohol formulation (6).

We designed the present study to compare the therapeutic efficacy of FML 0.1% acetate and 0.2% FML. In view of the double steroid concentration, we assumed that 0.2% FML might be more available to oc-

ular tissues after instillation than the 0.1% formulation (6). The results overlap, indicating that FML 0.1% acetate has much the same anti-inflammatory effect as 0.2% FML, leading to similar refractive outcomes. There were no significant differences in IOP-elevation potential.

As regards tolerance, patients did not complain of any symptoms except ocular dryness. This might be due to the high absorption of the drug (an "acetate" effect) and was resolved either by instilling tear substitutes, to provide immediate relief, or by reducing the daily administration in proportion to the anti-inflammatory efficacy. This last method merits further investigation.

We believe that the modest effects on IOP and the excellent local tolerance make FML 0.1% acetate as effective as FML 0.2% for the control of inflammation after PRK.

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