

# A randomised, double masked, clinical trial of high dose vitamin A and vitamin E supplementation after photorefractive keratectomy

Michele Vetrugno, Anna Maino, Giuseppina Cardia, Grazia Maria Quaranta, Luigi Cardia

## Abstract

**Aim**—To evaluate the effect of a high dose vitamin A and E supplementation on corneal re-epithelialisation time, visual acuity and haze following photorefractive keratectomy (PRK).

**Methods**—Two groups of 20 patients who underwent myopic PRK were supplemented with either 25 000 IU retinol palmitate and 230 mg  $\alpha$  tocopheryl nicotinate or a placebo. Clinical outcomes were evaluated up to 360 days.

**Results**—In the vitamin treated group, re-epithelialisation time was significantly faster ( $p=0.029$ ) and haze incidence was reduced ( $p=0.035$ ), especially for high myopic corrections ( $p=0.043$ ). This group also reported a significantly better uncorrected visual acuity ( $p=0.043$ ).

**Conclusions**—High dose vitamin A and E oral supplementation may accelerate re-epithelialisation time and may reduce corneal haze formation after PRK.

(Br J Ophthalmol 2001;85:537-539)

Corneal haze and myopic regression are the main undesirable complications after excimer laser treatment.<sup>1</sup> In the past few years, several authors indicated that keratocytes and epithelial cells are mainly involved in the healing response. In particular, it was suggested that the disappearance of anterior stromal keratocytes in response to excimer laser surgery was an initiating factor, which could lead to epithelial hyperplasia and eventually to haze formation and regression.<sup>2</sup> Wilson showed that anterior keratocyte death was mediated by apoptosis with little accompanying inflammation, while Shimmura indicated the generation of free radicals as the main cause of apoptosis, together with other triggers. In particular, the hydroxyl radical (OH•) was identified as the specific oxygen species of radicals formed by the excimer laser.<sup>3,4</sup>

The extent of tissue damage, therefore, may reflect the balance between the oxidative damage and the local antioxidation defence system and there is considerable experimental evidence on animals to support the use of pharmacological agents, which are specifically directed against the oxygen radicals that are formed during excimer photoablation or could influence corneal epithelial proliferation and differentiation.<sup>5,6</sup>

On this basis, we tried to verify the applicability of these data from animal models to the human cornea and we therefore

performed this study to determine whether the use of a high dose vitamin A and E supplementation could improve corneal re-epithelialisation, and reduce the incidence of haze and myopic regression after PRK.

## Materials and methods

Between February and April 1999, all patients requesting excimer laser surgery for myopia at the eye clinic, department of ophthalmology, University of Bari, Italy were considered eligible for the study. The independent ethic committee of the Policlinico, Bari, Italy, approved the study and written informed consent was obtained from all patients. Preoperative assessment consisted of a complete ophthalmic examination. Inclusion criteria were age ranging from 20–30 years, stable refraction for at least 2 years, myopia within  $-2$  to  $-10$  D, regular astigmatism and best corrected visual acuity higher than 0.2 reported on the logarithm of the minimum angle of resolution (logMAR) scale.<sup>7</sup> We excluded from the study patients with an history of ocular disease, previous refractive treatment, contact lens wear in the previous 2 months, intolerance to one of the components of the test capsules, wound healing abnormalities (for example, keloids), gastroenteric diseases, systemic diseases (especially diabetes, cardiac diseases and coagulation disorders because vitamin E could inhibit cytochrome P 450, enhancing the effects of insulin, digital and oral anticoagulants).<sup>8</sup>

Forty patients (40 eyes) met all the preoperative criteria and were randomly assigned either to the treated (vitamin group) or to the control group (20 patients each). The vitamin group received an oral supplementation of vitamin A (25 000 IU retinol palmitate) and vitamin E (230 mg  $\alpha$  tocopheryl nicotinate), (Evitex capsules, Alcon, Milan, Italy) whereas the control group was given a placebo capsule of the same colour and aspect.

## SURGICAL TECHNIQUE

All surgical procedures were performed by the same surgeon (MV), using Laserscan 2000 (Lasersight, Orlando, FL, USA), a flying spot excimer laser, whose technical features and surgical procedure are described elsewhere.<sup>9</sup> Corneal de-epithelialisation was carried out using a 20% alcoholic solution.

## POSTOPERATIVE SELECTION AND EVALUATION

On removal of the soft contact lens, all patients received a topical steroid treatment, dispensed four times a day for 1 month and therefore in

Eye Institute,  
Department of  
Ophthalmology-  
Otorhinolaryngology,  
University of Bari,  
Italy

M Vetrugno

A Maino

G Cardia

G M Quaranta

L Cardia

Correspondence to:  
Michele Vetrugno, MD,  
Istituto Clinica Oculistica,  
Università di Bari,  
Policlinico, piazza G Cesare,  
11, 70124 Bari, Italy  
[m.vetrugno@oftalmo.uniba.it](mailto:m.vetrugno@oftalmo.uniba.it)

Accepted for publication  
5 January 2001

Table 1 Re-epithelialisation time after PRK (2 day, 3 day, and 4 day time points) (number of eyes)

Study group	2 days	3 days	4 days
Vitamin group	13 (65%)	7 (35%)	—
Control group	6 (30%)	10 (50%)	4 (20%)
p Value*		0.029	

\* $\chi^2$  test p (p<0.05).

decreasing frequency every 3 weeks. In addition, every patient was instructed to self administer one test capsule three times a day for 30 days and then twice a day during the following 2 months. The oral supplementation was stopped together with the topical steroid drugs (about 90 days after PRK).

Postoperative examinations were repeated every 24 hours until re-epithelialisation occurred and then after 7, 30, 60, 90, 180, and 360 days after the laser treatment. Moreover, during the 90 day postoperative examination, a blood sample was taken from all patients. All blood samples were examined for biochemical variables such as alkaline phosphatase, triglycerides, calcium, vitamin A levels, and prothrombin time. We also asked all patients to disclose any side effect experienced after excimer laser surgery. As it was reported that chronic toxicity occurs after ingestion of 25 000 IU or more daily for "protracted" periods, we paid extra attention to characteristic clinical signs and symptoms, which are described elsewhere.<sup>9</sup>

#### STATISTICAL METHODS

All data were recorded in a spreadsheet and analysed using Winks Kwikstat (TexaSoft, Cedar Hill, TX, USA, software version 4.62). Continuous variables were compared by Student's *t* test for unpaired data whereas categorical variables were analysed by a  $\chi^2$  test.

Differences were considered statistically significant for probabilities less than 0.05 (two tailed test).

#### Results

No significant differences in age, sex, attempted myopic and astigmatic correction, and topographic irregularity were found. Corneal re-epithelialisation time was significantly decreased in the vitamin treated group compared with the control group (p=0.029), as shown in Table 1.

Table 2 summarises the changes in corneal transparency during follow up. Haze incidence was significantly reduced in the vitamin treated group (p=0.035). Dividing the sample according to the attempted myopic correction, no significant differences were noted for corrections

lower than -6 D (p=0.232), whereas less haze formation was found in the vitamin treated group for higher myopic corrections (p=0.043).

At the end of the study, the number of eyes with uncorrected visual acuity (UCVA) of 0 was greater in the vitamin treated group than in the controls (p=0.043).

The blood levels of alkaline phosphatase, calcium, triglycerides and the prothrombin time were all within the normal range and no differences between the two groups were noted. Vitamin A levels were significantly higher in the vitamin treated group compared with the control group (p<0.001) and they were also slightly elevated. Nevertheless, none of the patients reported any relevant side effect, except for two patients belonging to the vitamin treated group who reported sporadic episodes of insomnia during the first postoperative week.

#### Discussion

$\alpha$  Tocopherol reverses and prevents the effects of free radicals and enhances the intestinal absorption of vitamin A in humans. On the other hand, although vitamin A exerts a moderate antioxidant activity, it plays an essential part in epithelial growth and limbal stem cell differentiation, promoting corneal wound healing.<sup>10 11</sup> As slower tissue regeneration causes an increased risk of accumulation of oxidant inflicted damage in the tissue components, corneal re-epithelialisation time is crucial. In the present study, we noted that vitamins A and E significantly decreased re-epithelialisation time, haze formation, and myopic regression occurrence.

We assessed also the tolerance of the tested supplementation. Despite our vitamin treated group receiving high doses of vitamin A, no side effects were reported after 360 days and no clinical evidence of chronic retinoid intoxication was noted. We also determined prothrombin time for all patients, considering this value as indicator of probable vitamin E intoxication. All blood test results were in the normal range and no difference was noted between the vitamin treated group and the control group. This could be explained considering that simultaneous vitamin E administration eliminates some of the toxic effects of large doses of vitamin A. Moreover, it has also been reported that vitamin A toxicity is uncommon in adults who receive less than 30 mg of retinol per day (equivalent to 88 235 IU/day).<sup>9</sup> We could therefore assume that the tolerance of the association of vitamin A and E could be

<th> Table 2 Corneal haze assessment (360 days after PRK) related to myopic classes: number of eyes (%)

Haze (grading)	All patients		Low myopia (<-6 dioptres)		High myopia (>-6 dioptres)	
	Vitamin group (n=20)	Control group (n=20)	Vitamin group (n=9)	Control group (n=10)	Vitamin group (n=11)	Control group (n=10)
0	15 (75%)	9 (45%)	7 (35%)	7 (35%)	8 (40%)	2 (10%)
0.5	3 (15%)	1 (5%)	1 (5%)	—	2 (10%)	1 (5%)
1	2 (10%)	4 (20%)	1 (5%)	—	1 (5%)	4 (20%)
2	—	6 (30%)	—	3 (15%)	—	3 (15%)
p Value*		0.035		0.232		0.043

\* $\chi^2$  test p (p<0.05).

considered acceptable, even though further clinical studies are desirable.

In conclusion, this pilot study demonstrates that vitamin A and E administration in the first 3 months following excimer laser surgery significantly reduces the incidence of haze formation and myopic regression. This could confirm that free radical levels are an important determinant of the clinical outcome of excimer laser surgery. We therefore believe that concurrent antioxidant therapy may positively influence corneal wound healing after excimer laser keratectomy, although further studies are obviously required.

The authors have no proprietary interest in the development or marketing of any product or instrument mentioned in this article.

- 1 Epstein D, Fagerholm P, Nystrom HH, *et al.* Twenty-four month follow up of excimer laser photorefractive keratectomy for myopia. *Ophthalmology* 1994;**101**:1558–64.
- 2 O'Brien TP, Quian L, Aheaf MF, *et al.* Inflammatory response in the early stages of wound healing after excimer laser keratectomy. *Arch Ophthalmol* 1998;**116**:1470–4.
- 3 Wilson SE, He Y-G, Weng J, *et al.* Epithelial injury induces keratocyte apoptosis: hypothesized role for the interleukin-1 system in the modulation of corneal tissue organization and wound healing. *Exp Eye Res* 1996;**62**:325–38.
- 4 Shimmura S, Masumitsu T, Nakai Y, *et al.* Excimer laser-induced hydroxyl radical formation and keratocyte death in vitro. *Invest Ophthalmol Vis Sci* 1999;**40**:1245–9.
- 5 Brancato R, Schiavone N, Siano S, *et al.* Prevention of corneal keratocyte apoptosis after argon fluoride excimer laser irradiation with the free radical scavenger ubiquinone Q10. *Eur J Ophthalmol* 2000; **10**:32–38.
- 6 Wilson SE, Qian L, Weng J, *et al.* The Fas-Fas ligand system and other modulator of apoptosis in the cornea. *Invest Ophthalmol Vis Sci* 1996;**37**:1582–92.
- 7 Holladay JT, Prager TC. Mean visual acuity. *Am J Ophthalmol* 1991;**111**:372–4.
- 8 Rang HP, Dale MM, Ritter JM. Harmful effects of drugs. In: Rang HP, Dale MM, Ritter JM, eds. *Pharmacology*. 4th ed. Edinburgh: Churchill Livingstone, 1999:757–74.
- 9 Vetrugno M, Maino A, Cardia L. Prospective randomized comparison of simultaneous and sequential bilateral photorefractive keratectomy for the correction of myopia. *Ophthalmic Surg Lasers* 2000;**31**:400–10.
- 10 Marcus R, Coulston AM. Vitamins A, K, and E. In: Hardman JG, Goodman Gilman A, Limbird LE eds. *Goodman & Gilman's the pharmacological basis of therapeutics*. 9th ed. New York: McGraw-Hill, 1996:1573–88.
- 11 Kruse FE, Tseng SCG. Retinoic acid regulates clonal growth and differentiation of cultured limbal and peripheral corneal epithelium. *Invest Ophthalmol Vis Sci* 1994;**35**:2405–20.

#### Video Reports ([www.bjophthalmol.com](http://www.bjophthalmol.com))

Capsule staining and mature cataracts: a comparison of indocyanine green and trypan blue dyes. *D F Chang*

Pearls for implanting the Staar toric IOL. *D F Chang*

An intraocular steroid delivery system for cataract surgery. *D F Chang*



## A randomised, double masked, clinical trial of high dose vitamin A and vitamin E supplementation after photorefractive keratectomy

Michele Vetrugno, Anna Maino, Giuseppina Cardia, et al.

*Br J Ophthalmol* 2001 85: 537-539

doi: 10.1136/bjo.85.5.537

---

Updated information and services can be found at:

<http://bjo.bmj.com/content/85/5/537.full.html>

---

### References

*These include:*

This article cites 9 articles, 4 of which can be accessed free at:

<http://bjo.bmj.com/content/85/5/537.full.html#ref-list-1>

Article cited in:

<http://bjo.bmj.com/content/85/5/537.full.html#related-urls>

### Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

---

### Topic Collections

Articles on similar topics can be found in the following collections

[Epidemiology](#) (756 articles)

---

### Notes

---

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>