Superficial Automated Keratopigmentation for Iris and Pupil Simulation Using Micronized Mineral Pigments and a New Puncturing Device: Experimental Study

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Purpose: To study the outcomes and tolerance of micronized mineral pigments for corneal tattooing, using a superficial automated keratopigmentation (SAK) technique in an experimental animal model and a new puncture device to inject the pigments into the corneal stroma.

Methods: Forty eyes of 40 New Zealand rabbits were included in this study. The animals were divided into groups A and B. Both groups underwent SAK using a new automated keratopigmentation device. Micronized mineral pigments were injected through the epithelium into the corneal stroma to replicate the iris color in 25 eyes (group A), and black color was used to replicate the pupil in 15 eyes (group B). Slit-lamp examination was performed to evaluate the outcome. Histopathological examination was also performed to ascertain the presence of pigment dispersion, inflammation, and/or neovascularization.

Results: All 40 eyes showed good cosmetic appearance after keratopigmentation. No intraoperative complications were detected. At the first week, mild or moderated conjunctival injection was observed in 13 eyes and transitory corneal epithelial defects were also detected in 27 eyes. Examination was unremarkable 2, 4, and 6 months after surgery. No neovascularization was detected in any case in the histopathology study.

Conclusions: SAK using a new automated puncture device and micronized mineral pigments achieved good cosmetic outcomes for iris and pupil simulation. This method could be a valid alternative to treat serious cosmetic eye problems that affect the superficial cornea or functional problems, such as photophobia or diplopia secondary to iris defects or trauma.

Key Words: keratopigmentation, corneal surgery, cosmetic cornea, corneal tattooing, corneal puncturing device, micronized mineral pigments

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Galen (131–210 AD) is considered to be the first one to have used pigments in the human cornea, using reduced copper sulfate to mask corneal opacity.[1–3] Thereafter, keratopigmentation (KTP) gained limited popularity because of a variety of reasons. Various chemical products such as Indian ink, metallic powders, organic colors, animal uveal pigment, Chinese ink, gold and platinum chloride, and even soot were used.[4–7] The main problem that affected the outcome of previous KTP studies was the fading of the colors, which made results inconsistent with time.[3]

This problem has been reported to be solved using new micronized mineral pigments and improved intralamellar surgical techniques making the KTP procedure more reproducible and consistent.[8–10] Such pigments have been tested in different experimental and clinical studies with excellent results from cosmetic, histopathological, and immunological perspectives.[11–15] KTP has not only been used for cosmetic restoration for blind and phthisical eyes but also in patients with symptomatic glare associated with iris loss, atrophy, or trauma.[1,2,16–19] Also, in cases of disabling light scattering and photophobia in traumatic aniridia or iris coloboma[3,20] and even in treatment of incapacitating diplopia,[21] showing that this procedure may be used both in blind[8,22,23] and in sighted eyes, either for therapeutic or cosmetic purposes.[9,16–21]

Cosmetic contact lenses, enucleation, or evisceration are the most frequently used methods to improve the esthetic appearance in cosmetically unacceptable, disabled eyes.[24–26] However, there is enough evidence of the excellent outcomes using KTP, to achieve good cosmetic

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results and high patient satisfaction, avoiding extensive and mutilating reconstructive surgery.[8,9,16–23]

The corneal tattooing technique was performed traditionally as a manual procedure, and it was reported to be time consuming and associated with temporary or suboptimal results.[27] To obtain more precision and better outcomes in less time, it seems to be necessary to modify some instruments into ones that could make KTP a more accurate and reproducible technique. Femtosecond technology was recently introduced as a novel technological instrument for intrastromal KTP, showing good results to cosmetically restore eyes with cosmetic or functional disabilities.[16,18] However, to the best of our knowledge, for more than 6 decades, there have been no recent changes to improve the outcomes of the superficial KTP technique.[5]

The aim of this study was to investigate the outcomes and tolerance of selected micronized mineral pigments for iris and pupil reconstruction using the superficial automated keratopigmentation (SAK) technique with a new puncture device in an experimental animal model. As a secondary outcome measure, we investigated the safety of this new instrument.

MATERIALS AND METHODS

Experimental Animal Model

Forty eyes of 40 white New Zealand rabbits (only 1 eye from each rabbit was used for the study) with an average weight of 3 kg were used in this study. The anatomy and physiology of these eyes are considered to be very similar to human eyes. Animal care and treatment procedures were in accordance with the regular rules for experimental animal research of the animal laboratory at Miguel Hernandez University, Alicante-Spain (Real Decreto 53/2013). Ethics Committee approval was also received. The animals were randomly divided into groups A and B, and SAK was performed. The animals in group A (25 eyes) were treated simulating an iris with different colored pigments (peripheral pigmentation), and the eyes in group B (15 eyes) were pigmented in black to simulate a pupil (central pigmentation). The eyes were enucleated after euthanasia for histopathological examination to ascertain the presence of pigment dispersion, inflammation, or neovascularization in the ocular tissue.

Pigments

Specially selected micronized mineral pigments were used for this study. The colors used to simulate the natural color of the iris were green (B-CT40), dark brown (B-CT20), and light brown (B-CT30) in group A (Fig. 1A). A black pigment (B-CT05) was also used in group A to simulate the iris (Fig. 1A). A black pigment (B-CT05) was used to simulate the pupil in group B. The micronized mineral pigments, black, green, brown, and light brown, are composed of varying amounts of propanediol, lactic acid, and micronized pigments (CI: 77007, 77499, 77491, 77492, 77891, and 77288) found in the list of permitted colorants in cosmetics according to the Ministry of Health and in accordance with Annex IV of European Regulation of Cosmetics (BioChromaEyes, Blue Green Company, Spain).

Superficial Keratopigmentation Device

This new device allows the color to be introduced automatically into the anterior corneal stroma (Fig. 1B). KTP

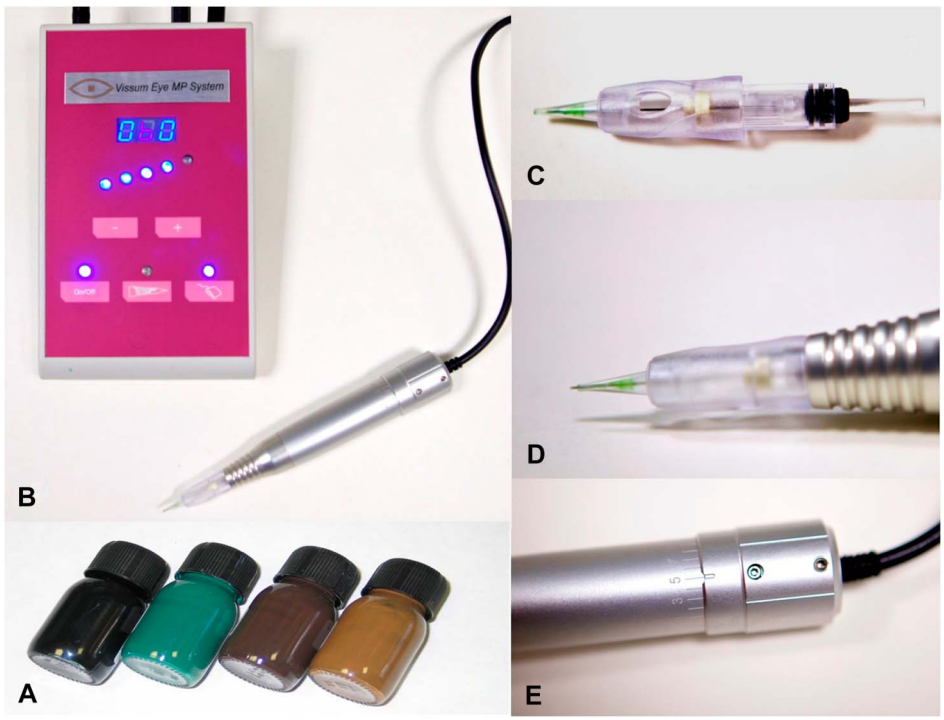

FIGURE 1. A, Bottles of the different colors of pigments used. From left to right: black (B-CT05), green (B-CT40), dark brown (B-CT20), and light brown (B-CT30). B–E, Vissum eye MP system device for SAK, (B) automated device with the handpiece, (C) disposable tip with 3 needles (N°3) before being inserted in the handpiece, (D) handpiece showing the disposable tip (N°3) with 3 needles inside ready to be used, (E) rotating handle piece to select the punch depth (11 positions available).

was performed using a new puncture device (Vissum Eye MP System, Madrid, Spain; Apl. No.2.949.539, provided by Blue Green Company, Spain), and automatic micropunctures were performed, puncturing the superficial layers of the stroma to an approximate depth of 120 μm from the corneal surface. The penetration depth of the needles is controlled by the length of the longitudinal axial vibration of the tip (Fig. 1E). There are also different tips, with different numbers of needles that can be used depending on the area that is going to be treated (Figs. 1C, D). For limbus or pupil simulation, we used the tip with only 1 needle (Nº1), and for iris simulation, we used a tip with numerous needles (Nº3 or Nº5) (Blue Green Company, Spain).

Superficial Automated Keratopigmentation

The animals were anesthetized with a subcutaneous injection of a 1:1 mixture of 40 mg/kg ketamine hydrochloride (Imalgene 1000; Merial, Lyon, France), 10 mg/kg xylazine hydrochloride (Xilagesic 2%; Laboratorios Calier, Barcelona, Spain), and ocular topical double anesthetic (tetracaine 0.1% and oxybuprocaine 0.4%, Colircusi; Alcon Cusi S.A., Barcelona, Spain). Eyes were positioned and stabilized, and a lid speculum was used. The eyes from group A, in which iris simulation was planned, were treated with the peripheral superficial corneal KTP technique with different colors to mimic the iris, using a prototype of a puncture device (Vissum Eye MP System, Madrid, Spain; Apl. Nº 2.949.539). The center of the cornea was marked with a caliper, and the pupil size determined by an optic zone marker (Katena, New York). Then, automatic micropunctures were performed to inject the pigments into the superficial layers of the stroma, leaving the pupillary area clear (Fig. 2B). This maneuver was repeated until an adequate amount of pigment was deposited in the superficial stroma to achieve the desired color (black, green, brown, or light brown) and shape of iris. This pigmented area was centrally delimited by the circle previously marked with the optic zone marker and peripherally by the limbus. The same procedure was then performed in group B, in which pupil simulation was planned using only the black pigment. In this group, the pigment was injected inside the area marked with the optic zone marker of 6 mm (Fig. 2C).

Postoperative Treatment

Antibiotic prophylaxis was topically applied using chloramphenicol eye ointment (Chloramphenicol, Alcon Cusi S.A., Barcelona, Spain) twice a day for 7 days, and tobramycin/dexamethasone 3 mg/mL +1 mg/mL (Tobradex, Alcon Cusi S.A., Barcelona, Spain) twice a day for 7 days. Cyclopentolate hydrochloride 10 mg/mL (Colircusi cycloplegic, Alcon Cusi S.A., Barcelona, Spain) was also applied topically twice a day for 3 days. Additional prophylactic actions were taken to avoid infection using immediately postoperative tobramycin eye ointment 3.5 g (Tobrex, Alcon) and gamma radiation of the mixtures as preoperative sterilization of the pigments. Subcutaneous buprenorphine injection 0.05 mg/kg 2 times daily and paracetamol 100 mg/100 mL in drinking water for 7 days were also given to control postoperative pain.

Postoperative Clinical Cosmetic Outcome Evaluation

Examination under a surgical microscope (Takagi OM-5, Nakano, Japan) was performed daily during the first week and once a week during 2 weeks; then, 1, 2, 3, 4, and 6 months after surgery. Photographs were taken at each visit to detect any change in the appearance of the eyes treated. A portable slit-lamp (Kowa SL-15, Duesseldorf, F.R. Germany) and drops of fluorescein sodium 1% (Bausch & Lomb, Australia) were used to detect corneal epithelial defects. The anterior segment examination also included conjunctival injection, corneal haze, corneal neovascularization, and corneal infiltrates. Cosmetic appearance after surgery was evaluated by an ophthalmologist of the investigator team but different from the surgeons who performed the procedures. This ophthalmologist made the evaluation of the surgical result taking into account the scale shown in the

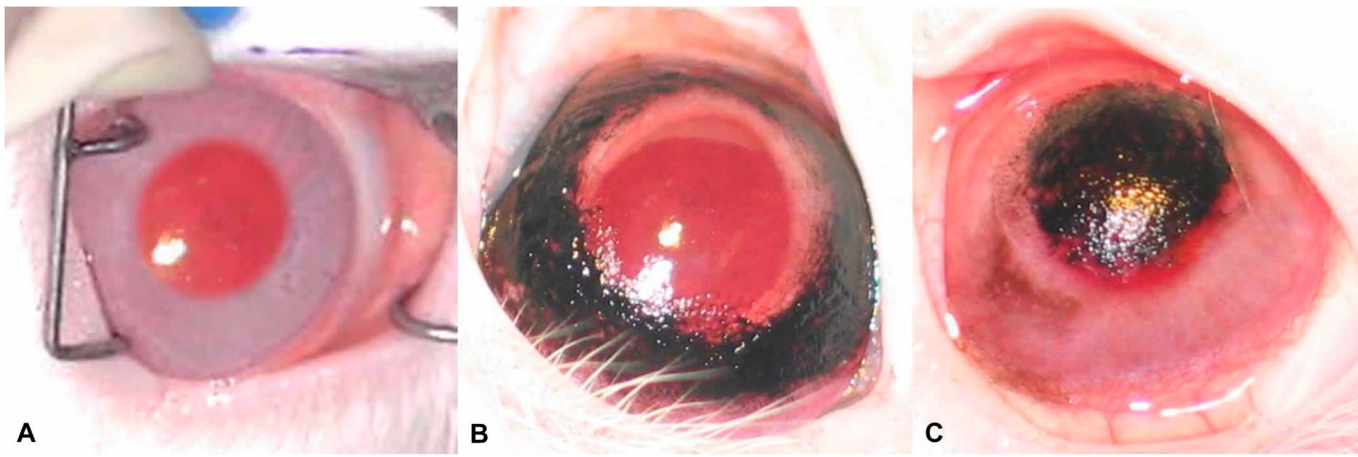

FIGURE 2. A, Eye of a rabbit before KTP surgery. B, Peripheral KTP of the cornea simulating the iris. C, Central KTP simulating the pupillary area.

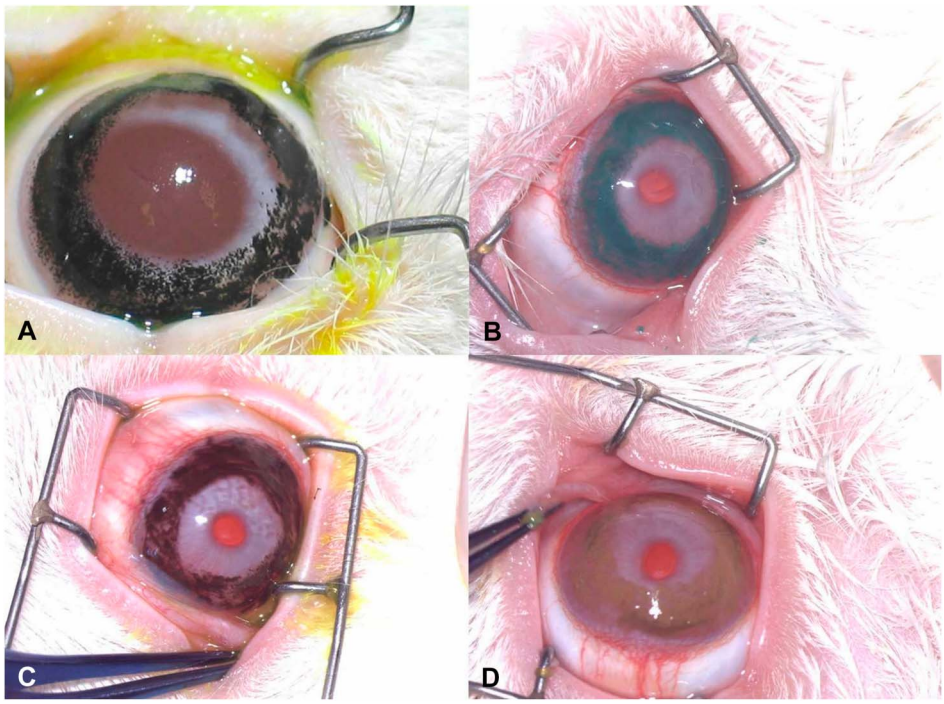

FIGURE 3. Rabbit eyes showing the different colors used. Black (A), green (B), dark brown (C), and light brown (D).

Supplemental Digital Content 1 (see Table 1, http://links.lww.com/ICO/A529). Other complications, such as abscesses, infection, melting, calcification, and ulcers were also evaluated.

Histopathological Analysis

The eyes were enucleated 6 months after surgery and placed in Davidson liquid for 48 hours and then placed in 70% ethanol until tissue processing. Each cornea was embedded in 6 paraffin blocks and sectioned in microslides (4 μm) with a microtome. Sections were stained with hematoxylin–eosin to determine the presence and distribution of inflammatory cells (lymphocytes, macrophages, and neutrophils) surrounding the pigment. Any inflammatory infiltrate was described as acute or chronic on the basis of its cellular composition. The presence of neovascularization and pigment diffusion was also documented if present. The results were evaluated for each one of the pigments.

RESULTS

Surgical Procedure

All cases were operated without complications. Particularly, no perforations or problems related to the surgical procedure were observed in any of the cases in the study either intraoperatively or postoperatively.

Cosmetic Experimental Outcome

The cosmetic outcome was evaluated by an ophthalmologist who determined the assessment of the eyes treated classifying them according to the cosmetic appearance: 0: unsatisfactory, 1: acceptable, 2: good, and 3: excellent. All eyes of treated rabbits were classified as having an excellent cosmetic result (score 3), except for 5 eyes that had a score of 2 (good cosmetic but less than ideal). None of the eyes were rated 0 or 1 (unsatisfactory or acceptable).

Clinical Biomicroscopy Outcomes

All the eyes treated and completing the study showed excellent cosmetic appearance at the end of the study. One animal was prematurely killed because of a neurological problem, which was not related to the study.

Slit-lamp examination 7 days after surgery showed the following results: 67.5% (27 eyes) did not show any sign of conjunctival injection; 15% (6 eyes) presented conjunctival injection of grade 1 and 17.5% (7 eyes) presented conjunctival injection of grade 2; 22.5% (9 eyes) presented epithelial defects of grade 1, 32.5% (13 eyes) grade 2, and 12.5% (5 eyes) grade 3. The total of eyes with epithelial defects 7 days after surgery was 67.5% (27 eyes). However, the epithelial defect was already resolved by that time in 13 eyes (32.5%). A low grade of corneal haze (grade 1) was observed in 2 eyes (5%). No signs of neovascularization, changes in color, or corneal infiltrates were seen in any eye treated.

Examination 2 months after surgery showed the following results: in 87.5% of the eyes, the conjunctival injection was completely resolved. Only 12.5% of the eyes had conjunctival injection of grade 1. Regarding the epithelial defects, only 3 eyes (7.5%) had defects of grade 1 and 2 eyes (5%) grade 2. The rest of the variables studied were within normal limits.

Examination showed excellent cosmetic appearance with no ocular surface inflammation 6 months after KTP.

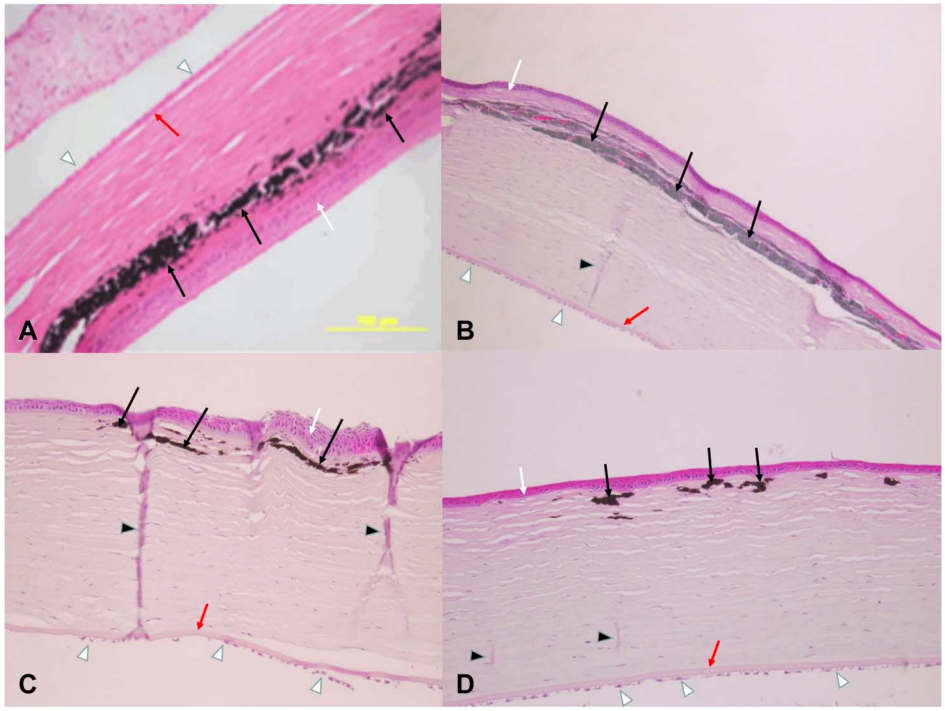

FIGURE 4. Hematoxylin–eosin staining of the SAK technique in the rabbit's eyes. Each photograph corresponds to black (A), green (B), dark brown (C), and light brown pigments (D). Dark stain, parallel to the corneal surface, of variable length and thickness, which appears to be located between the stromal collagen lamellae and in the more superficial stroma (black arrows). In the upper portion of the cornea, we can see the epithelium (white arrows) and in the inferior portion of the tissue, the endothelial cells (white arrowheads) lying just under Descemet membrane (red arrows). Pink lines appearing in the preparations are folds in the tissue created during the process (black arrowheads).

No conjunctival injection, epithelial defects, corneal haze, corneal infiltrates, changes in color, or neovascularization were observed. The pigmented corneas showed good cosmetic appearance without changes in color or dispersion of the pigments in the animals treated in groups A and B (Fig. 3).

Histopathological Results

The histopathological study was performed 6 months after pigmentation. Microscopic examination was also performed, and it demonstrated the permanence of the pigments applied in all the eyes treated (Fig. 4). No inflammation, fibrosis, scarring, or neovascularization were found in any of the eyes from group A (iris simulation group) or group B (pupil simulation group). The pigments remained in the superficial corneal stroma, between 50 and 150 μm of depth, without dispersion in all cases except 2, in which the pigmented area reached not only the superficial stroma but also the mid corneal stroma. No perforations were observed in any eye treated. The keratocytes near the pigmented area were activated, and some had very small particles of pigment in their cytoplasm. However, no atypia was detected in these cells. The corneal epithelium was within normal limits in all cases. The stroma showed the normal wavy arrangement of the collagen fibers, and examination of the endothelium was unremarkable (Table 1).

DISCUSSION

KTP has been used by ophthalmic surgeons for centuries, as an attempt to restore the cosmetic appearance of severely impaired eyes. Its use for restoration of visual problems in patients with visual disabilities related to iris defects due to aniridia, trauma, and even in cases of monocular diplopia has also been reported.[1–3,5,6,16–21] Other alternatives could also be considered, such as iris prostheses in sight-compromising iris defects.[28]

An experimental animal model was used in this study to simulate an iris and a pupil on the corneal surface (superficial stroma), using different micronized pigments and a new automated KTP device. The procedure of the previously

TABLE 1. Clinical and Histopathological Parameters

Clinical Examination Anterior Segment	Grade	Histological Study	Grade
Conjunctival injection (A)	0–3	Inflammation (F)	0–3
Epithelial defect (B)	0–3	Neovascularization (G)	0–3
Corneal neovascularization (C)	0–3	Pigment diffusion	Yes/no
Corneal haze (D)	0–3		
Corneal infiltrates	Yes/no		
Changes in color	Yes/no		
Cosmetic appearance (E)	0–3		

A → 0: normal; 1: mild reddish color; 2: bright red; 3: deep, bright redness.
B → 0: none; 1: area ≤25 mm^2; 2: area 26–99 mm^2; 3: area ≥100 mm^2.
C → 0: no neovascularization; 1: new vessels appear on the peripheral cornea; 2: new vessels appear but not invading the center of the cornea; 3: new vessels invading the central cornea.
D → 0: clear cornea; 1: mild (iris details clearly visible); 2: moderate (iris details not clearly visible); 3: severe (opacification, without view of the anterior chamber).
E → 0: unsatisfactory (when the result was cosmetically unacceptable); 1: acceptable (when the result was cosmetically acceptable); 2: good (when the cosmetic result was less than ideal); 3: excellent (when the result was cosmetically ideal).
F → distribution of inflammatory cells (lymphocytes, macrophages, and neutrophils) surrounding the pigment. 0: normal; 1: mild; 2: moderate; 3: severe.
G → presence of new vessels in the cornea. 0: none; 1: mild; 2: moderate; 3: severe.

described KTP technique used in clinical cases was followed for the purpose of this experimental investigation.[8,17] Micronized mineral pigments have demonstrated good cosmetic results with corneal tolerance and biocompatibility in previous studies.[12–15]

This superficial and intrastromal KTP technique has shown excellent cosmetic and functional results, in experimental and clinical models previously published by our group.[8,12–15,17] We believe that it could be also a valid alternative to avoid cosmetic prosthesis and cosmetic shells or contact lenses.

One of the advantages of this technique is the possibility to achieve different depths using different needles that could cover different depths of scars. Taking into consideration that the thickness of the human cornea is normally between 500 and 550 μm, the depth at which KTP is performed is adjusted perfectly. Therefore, the cornea is pigmented without any perforation risk. We believe that another important advantage is that this technique allows the pigments to be introduced into the superficial stroma. When the pigment is introduced below the corneal epithelium, it could also favor its retention within the stroma. However, if the pigment is close to the superficial transitional epithelium, there could be a higher risk of fading because of frequent cell regeneration on this area of the cornea.

Micronized mineral pigments can also be mixed to achieve any iris color. The small size of the mineral particles due to the micronization process could also decrease the possibility of foreign body reaction. This was studied from the histopathological and immunopathological point of view.[15] Availability of different colors is important to mimic a normal iris, and the black color could simulate the pupil's normal color and reflect quite well. Also, the new automated KTP device could also make the surgery less time consuming, as it could introduce the pigments more quickly into the superficial stroma.

In this study, no complications such as neovascularization, inflammation, perforation, pigment migration or diffusion, pigment degradation, or changes in color were found in this experimental model. The pigments were stable in the corneal tissue throughout the study period. It should also be considered that the results herein described are limited to these types of mineral pigments and may not be extrapolated to other pigments with a different composition. The pigment particles placed at the corneal plane may allow stray light to enter obliquely in sighted eyes causing a reflecting effect, but in clinical practice, this type of surgery using the superficial automated device would be performed in patients with corneal opacity without vision. Furthermore, we did not observe any fading of these pigments in the corneas of the animals. This could possibly be due to the 6-month time limit of this study. However, fading of these pigments may occur with longer periods of time.

In conclusion, no evidence, either clinical or histopathological of local toxicity, was found in corneas colored using the micronized mineral pigments selected for this experimental investigation, which suggests that they could be a valid alternative for KTP. In this study, the superficial KTP technique and the new puncture device to introduce the pigment into the corneal stroma have demonstrated to be precise for iris and pupil reconstruction. These procedures could provide great cosmetic improvement when applied on human eyes with serious incapacitating symptoms secondary to severe visual function disabilities related to iris defects and intractable diplopia and also in eyes with no visual prognosis and unaesthetic appearance.

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